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TOPICAL COMPOSITION CONTAINING HYALURONIC ACID AND NSAIDS
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- (57) Claim

1. A pharmaceutical composition comprising a plurality of effective non-toxic dosage amounts of a composition, each such dosage amount comprising a therapeutically effective non-toxic dosage amount of a drug for the treatment of a disease or condition of the skin or exposed tissue at the site of the pathology or trauma and an effective non-toxic dosage amount of at least 5mg/cm² of a form of hyaluronic acid selected from hyaluronic acid and salts thereof to transport the drug to the site of the pathology or trauma of the disease or condition, wherein the molecular weight of the form of hyaluronic acid is less than 750,000 Daltons and greater than 150,000 Daltons.

TITLE OF INVENTION

TREATMENT OF DISEASE EMPLOYING HYALURONIC ACID AND NSAIDS.

FIELD OF INVENTION

5 This invention relates to the treatment of disease
and conditions of the skin and exposed tissue. In some
embodiments this invention finds application to the treatment
of a disease or condition of the skin and exposed tissue
including basal cell carcinoma, squamous cell tumours,
metastatic cancer of the breast to the skin, primary and
10 metastatic melanoma in the skin, malignancies and tumours in
the skin, genital warts (condyloma acuminata), cervical
cancer, HPV (Human Papilloma Virus) including HPV (Human
Papilloma Virus) on the cervix, psoriasis (both plaque-type
psoriasis and nail bed psoriasis), corns on the feet, actinic
15 keratoses lesions, "liver" spots, fungal lesions, and other
such types of lesions, and hair loss on the head of a
pregnant women.

This invention also relates to compositions and
formulations suitable for use in such treatments, the use of
20 such formulations in such treatments, methods of such
treatment, and the delivery of drugs for such treatments.

BACKGROUND OF THE INVENTION

Basal cell carcinoma is presently treated by
surgery. Each lesion, together with all surrounding and
25 underlying tissue (dermis, epidermis, and subdermis), is cut
out. In some instances, surgery, while necessary for the
patient's welfare, puts the patient at risk in some other
respect (for example, the removal of a lesion on a patient's
temple (resection) may jeopardize the patient's health).
30 Squamous cell tumours are also treated the same way as are
other forms of cancer in the skin and exposed tissue.
Furthermore, other conditions and diseases of the skin and
exposed tissue are treated in the same way or in ways that
cause discomfort to the patient, for example melanoma, genital
35 warts, cervical cancer, HPV (Human Papilloma Virus).

Actinic keratoses lesion is dealt with similarly.
Liquid nitrogen is also used to remove the lesion.

These diseases and conditions are usually found in
the epidermis (at least for the most part, extending into the
40 dermis and upwards through the Stratum Corneum).

Hyaluronic acid is a naturally occurring glycosaminoglycan. Its molecular weight may vary from 50,000 daltons upwards, and it forms highly viscous solutions. As regards the actual molecular weight of hyaluronic acid in natural biological contexts, this is still a matter of much uncertainty; when the molecular weight of hyaluronic acid is to be determined, different values are obtained depending on the assay method employed, and on the source, the isolation method etc. The acid occurs in animal tissue, e.g. spinal fluid, ocular fluid, synovial fluid, cockscombs, skin, and also in some streptococci. Various grades of hyaluronic acid have been obtained. A preparation with an allegedly high degree of purity and alleged to be entirely free from side effects, is a non-inflammatory form described in U.S. Patent No.4,141,973; this preparation is said to have a molecular weight exceeding 750,000 dalton, preferably exceeding 1,200,000 dalton and is suggested for therapeutic use in various articular conditions. Applicants believe that hyaluronic acid claimed in this patent is sold under the trade mark Healon.

United States Patent 4,801,619 relates to hyaluronic acid, having a molecular weight of about 3×10^6 dalton or more, administered intra-articularly which is prone to decrease the proteoglycan content of synovial fluid to almost normal levels. According to this patent, this indicates a positive effect on the proteoglycan metabolism of a joint. According to the patent, this is applicable both to inflammatory conditions and to degeneration caused by treatment with symptomatics, such as corticosteroid preparations. It is thus clear that a sufficiently high molecular weight of the hyaluronic acid is alleged to counteract side effects that might be caused by corticosteroids or other symptomatics producing similar effects. When corticosteroids are applied, the amount of hyaluronic acid in the synovial cavity will, according to the patent, increase substantially and, according to the inventors, their hyaluronic acid preparations have a very positive effect on such clinical symptoms as pain, swelling, and lameness.

The patent states that the objectives of the invention are attained by intra-articular administration (injection) of an effective amount of hyaluronic acid with a mean molecular weight exceeding 3×10^6 dalton, preferably exceeding 4×10^6 dalton; usually the molecular weight will not exceed 7×10^6 dalton. The dosage of hyaluronic acid administered is stated to be preferably within the range of 5mg-80mg. The amount of solution given at each administration is generally less than 60 ml, e.g. less than 20 ml. of an aqueous solution of the acid or its salt. It is convenient to administer the acid dissolved in water (<2% w/w, buffered to physiological pH), for instance in the form of a water-soluble sodium salt. The exact amount will depend on the particular joint to be treated.

The Merck Index Specifies that Hyaluronic Acid has a Molecular Weight within the range pf 50,000 to 8×10^6 depending on source, methods of preparation, and methods of determination. The Merck Publication teaches hyaluronic acid as a surgical aid (ophthalmological).

United States Patent 4,808,576 purports to teach that hyaluronic acid, an agent well known for reducing the sequelae of trauma in mammalian joint tissue when injected directly into the traumatized joint tissue, will be carried to such traumatized tissue by the mammal's natural processes if applied at a site remote from the traumatized tissue. Thus, hyaluronic acid in any therapeutically acceptable form can, according to the Patent, be administered by the typical remote routes including intravenous, intramuscular, subcutaneous, and topical.

This, the patent alleges, makes the utilization of hyaluronic acid much more convenient and attractive. For instance, the treatment of arthritis in horse or human joints with hyaluronic acid, according to the patent, no longer requires more difficult intra-articular injections.

United States Patent 4,725,585 relates to a method of enhancing or regulating the host defence of a mammal by administering to a mammal a therapeutically effective amount of hyaluronic acid.

At column 1, lines 43 - 46, the patent provides that the invention was based on the unexpected discovery that administration of hyaluronic acid to mammals results in a considerable increase in the defence.

5 The hyaluronic acid employed in the patent was Healon (t.m) provided by Pharmacia AB, Uppsala, Sweden (Pharmacia AB is also entitled to the benefit of United States Patent 4,141,973). The patent provides at column 4, line 19 that because a patient's infections had been hard to treat,
10 instead of just hyaluronic acid being administered to the patient to increase the patient's defence, the patient was given hyaluronic acid and an antibiotic. While one reading the patent may conclude that the antibiotic was given in combination with hyaluronic acid, in fact because the
15 hyaluronic acid was administered subcutaneously and because the patient was a heart patient, one skilled in the art would understand that any antibiotic administered, while possibly administered simultaneously with the administration of the hyaluronic acid, was definitely administered separately
20 intravenously (probably) or intramuscularly (less probably). Thus, the hyaluronic acid administered, according to the teachings of this patent, was administered in order to prevent possible development of infections (increase the host's defence) and not for any other reason.

25 United States Patent 4,636,524 discloses cross-linked gels of hyaluronic acid, alone and mixed with other hydrophilic polymers and containing various substances or covalently bonded low molecular weight substances and processes for preparing them. These products are alleged to
30 be useful in numerous applications including cosmetic formulations and as drug delivery systems.

 The patent further states that as hyaluronic acid is known to be a biologically tolerable polymer in the sense that it does not cause any immune or other kind of response when
35 introduced into a human body, the cross-linked hyaluronic acid gels can be used for various medical applications. The cross-linked gels modified with other polymers or low molecular weight substances, it is alleged, can be used as drug delivery devices. For example, the inventors are alleged to have

found that heparin introduced in a cross-linked hyaluronic acid gel retained its antithrombogenic activity.

The inventors also allege that they have also found that cross-linked gels of hyaluronic acid can slow down the release of a low molecular weight substance dispersed therein but not covalently attached to the gel macromolecular matrix.

Unites States Patent 4,736,024 purports to teach new medicaments for topical use containing:

(i) an active pharmacological substance or a mixture of pharmacological substances, either active or suitable for topical administration and

(ii) a topical vehicle which comprises hyaluronic acid or a molecular fraction of hyaluronic acid or a salt of the same with an alkaline metal, an alkaline earth metal, magnesium, aluminium, ammonium, or a pharmacological substance optionally together with additional conventional excipients for pharmaceutical preparations for topical use.

Applicants are also aware of published Japanese Patent Document 61000017, dated 86/01/06, whose English abstract of disclosure states that the Japanese Patent Document relates to the use of hyaluronic acid or cross-linked hyaluronic acid or their salts as the active ingredient for inhibiting carcinoma metastasis.

According to the purported abstract of the patent, more than 1.0% of hyaluronic acid is dissolved in alkaline aq. soln. and pref. more than 50% of H₂O sol. org. solvent. eq. alcohol, acetone, dioxane, against total soln. is added. Preferably the pH is 12-14. Then a multifunctional epoxy cpd. is added and reacted at 10-60 deg. C, pref. at 20-40- deg. C for 24 hrs. Cross-linking ratio of crosslinked hyaluronic acid or its salt is regulated by changing mol ratio of hyaluronic acid or its salt and multifunctional epoxy cpd.. Pref. hyaluronic acid used has intrinsic viscosity 0.2-30, m.w. 4000-2000000. The hyaluronic acid is allegedly used in several dosage forms. The clinical dose for an adult is alleged to be normally, as hyaluronic acid or cross-linked hyaluronic acid, 25mg-5 g/day (p.o.) and 10 mg-2.5 g/l dose (inj). The abstract alleges that the advantage is that the hyaluronic

acid has no side effects as may other anti-cancer drugs and has an analgesic and a tissue restoration effect.

European Patent Application 0295092 purports to teach a vehicle together with fragments of hyaluronic acid for delivering of the fragments of hyaluronic acid into the skin to reach the dermal layer of the skin to increase the development of blood vessels for stimulating hair growth or regrowth. The preferred fragments of hyaluronic acid are polysaccharides containing from 7 to 25 monosaccharide units. The patent provides that it is apparent that the larger the fragments of hyaluronic acid, the greater the difficulty there is in delivering the fragments to the dermal layer of the skin, unless there is also present in the composition a means for enhancing the activity of said fragments.

The combination may thus include a means for enhancing the activity of the fragments of hyaluronic acid, especially to improve their penetration through the skin following topical application. Some activity enhancers, it is alleged, also function as vehicles for the fragments of the hyaluronic acid.

Some activity enhancers are also alleged to possess the ability to stimulate or increase hair growth. Minoxidil is asserted among others to be such an activity enhancer. Thus both the fragments of hyaluronic acid and minoxidil are alleged to stimulate hair growth both delivered by a vehicle.

European Patent Application 0179442 asserts that where free radicals are formed in considerable quantities, hyaluronic acid is broken down or degraded before the hyaluronic acid has given the desired effect.

Canadian Letters Patent 1,240,929 teaches the combination of chondroitin sulfate compound and a hyaluronate to protect both human and animal cell layers and tissue subject to exposure to trauma.

European Patent Application 0208623 purports to teach hyaluronic acid as "une augmentation de l'activité de certaines proteases". It also purports to teach the use of hyaluronic acid for treating connective tissue diseases, including malignant tumours and cardiovascular disorders.

European Patent Application 270317 purports to teach the combination of an antiviral agent lacking inhibitory action and a compound [for example, hyaluronic acid] possessing cell fusion inhibitory activity and/or virus-adsorption inhibitory activity for treating disease carried by a virus.

United States Patent 4,840,941 purports to teach the use of an effective amount of hyaluronic acid as the active agent for the treatment of retroviruses in association with a pharmaceutically acceptable carrier, diluent, or excipient.

United States Patent 4,851,521 and European Patent Application 0265116 both describe hyaluronic acid fractions, the making thereof and cross-linked esters of hyaluronic acid incorporated into pharmaceutical preparations as the active ingredient and as vehicles for ophthalmological medicines for topical use (See column 11, lines 35 to 42; and column 12, lines 62 to column 13, line 3) and in suppositories for a systemic effect due to the effect of transcutaneous absorption, such as in suppositories.

The patent provides at column 13, lines 5 to 31:

"The vehicling action of the hyaluronic esters also applies to associated medicaments of the type mentioned above in which the active substance acts not only topically or by nasal or rectal absorption, for example by nasal sprays or preparations for inhalation for the oral cavity or the pharynx, but also by oral or parenteral route, for example by intramuscular, subcutaneous or intravenous route, as it favors absorption of the drug into the application site. The new medicaments can therefore be applied, apart from in the fields already mentioned, in practically all sectors of medicine, such as internal medicine, for example in pathologies of the cardiovascular system, in infections of the respiratory system, the digestive system, the renal system, in diseases of an endocrinological nature, in

oncology, in psychiatry etc., and may also be classified therefore from the point of view of their specific action, being perhaps anesthetics, analgesics, anti-inflammatories, wound healers, antimicrobics, adrenergic agonists and antagonists, cytostatics, antirheumatics, antihypertensives, diuretics, sexual hormones, immunostimulants and immunosuppressants, for example, one of the drugs having the activity already described for the therapeutically active alcohols to be used as esterifying component according to the present invention, or for the therapeutically active bases used for the salification of the free carboxylic groups."

There have been extensive studies to determine the defect in immune function that allows a tumour cell to develop. It was postulated initially by Jerne, and subsequently by Burnett, that the immune system's major role was that of immunological surveillance to destroy abnormal cells. The concept of surveillance, while somewhat simplistic, remains an accepted concept for the elaborate mechanism of immune recognition and function that is present in the higher species - mammals.

It has then been postulated that tumours develop because of local or generalized immune suppression. However, as pointed out by Moller, if general immune suppression occurs, it is only certain types of neoplastic disorders that develop, mainly those of the lympho-reticular system. This observation is generally correct and represents a major challenge to the immune surveillance theory unless a specific reason can be shown as to why the individual cancer cell can develop plus individually evade the immune system.

It was demonstrated experimentally in 1974 that defects of macrophage function may exist in neoplastic disease.

The initial experiments found suppressor cells to be part of the immune system; these were either of the T-cell type of the macrophage cell system. There was presence

demonstrated in neoplasia, chronic bacterial infection, recovery from massive injury and chronic fungal infection.

There has been repeated demonstration in experimental animals that the macrophage cell function is altered in neoplastic disease. The macrophages in the animal's systems appeared "blocked" in their function. Generally when removed from the *in vivo* situation, washed in saline and cultured, they perform normally. This block has been shown to be related to the excessive production of prostaglandin by neoplastic tissue or by the macrophage itself. Similarly, the N.K. cells (which are said to be primitive or immature macrophages and which may be involved in cancer defence) are also blocked.

In the basic research efforts in the latter '70s and the early '80's, there existed considerable confusion as to what role immunotherapy should take in cancer. Activation or "hyping" of macrophages was thought to be important. However, in an examination by Romans and Falk of peritoneal macrophages obtained from patients with neoplastic disease, there was definite evidence that these macrophages were already activated yet were co-existing with cancer cells and not causing their destruction.

It has recently been shown by several independent investigators that the malfunction of macrophages or the putitive block is due to excessive prostaglandin and that this can be altered in tissue culture by corticosteroids, ASA, and the non-steroidal anti-inflammatory drugs, i.e. indomethacin and naproxen (Naprosyn™). Again, it was repeatedly demonstrated that in animal tumours these substances could alter the response to neoplastic cells and that various combinations of these substances employed with immune enhancing agents could produce very credible success in eliminating experimental tumours. Lala and co-workers combined Indomethacin therapy with Interleukin 2 and showed that this could effect a cure with experiment neoplasm.

There were continued problems with the use of any of these agents in the actual human *in vivo* experience. All of the non-steroidal anti-inflammatory agents (NSAID) produced major toxicity in terms of gastro-intestinal, neurological,

and other areas. Thus, the basis of the present approach is that, under general circumstances, with the use of these agents in human disease in sufficient amounts, the drug will penetrate to any pathological tissue to alter therapeutically local prostaglandin production. While intravenous preparations of Indomethacin (and now of other agents) exist, using these drugs alone produces prohibitive side effects in human subjects. Therefore, only insufficient amounts can be brought into the body to effect more than occasional responses in neoplasm.

However, the majority of the evidence is present to indicate and therefore, it can be postulated that the basis for neoplastic development and how the initial cell "sneaks by" the immune surveillance mechanism relates to its production of prostaglandin. One need postulate only one mutation to alter the amount of prostaglandin synthesis produced by cells when they become "malignant" to establish a mechanism of blocking out the initial cell in any immune reaction, i.e. the macrophage. It therefore became essential to develop a combination of NSAIDs for clinical use to produce a major improvement in response in neoplastic disease and other conditions where excessive prostaglandin synthesis represents the basis of the pathogenesis of this disease state, i.e. arthritis and various others of the so-called connective tissue inflammatory disorders and/or auto-aggressive diseases.

See also:

1. Modulation of Immunity in Cancer Patients by Prostaglandin Antagonists, Immunity to Cancer II, Alan R. Liss, Inc.; and
2. Goodwin, J.S., (1981) Prostaglandin E and Cancer Growth Potential for Immunotherapy with Prostaglandin Synthesis Inhibitors, Augmentive Agents in Cancer Therapy, Raven Press, New York.

United States Patent 4,711,780 teaches a pharmaceutical composition comprising Vitamin C, a zinc salt, and a sulfur amino acid for treating surface epithelium for epithelium regeneration. Hyaluronic acid may be added for

applications in the reproductive tract to block the passage of toxins into the blood system.

U.S. Patent 4,937,254 (Ethicon) teaches combinations of hyaluronic acid and salts thereof with NSAIDS for the prevention of adhesions after surgery.

Because of the side effects of the use of non-steroidal anti-inflammatory drugs (major toxicity in terms of gastro-intestinal, neurological, and other areas), use thereof should also be restricted (if possible) to the area of use without delivery to other areas which are not in need of treatment. Thus, if useful amounts of the non-steroidal anti-inflammatory drugs or for that matter any drugs could be delivered to a site in need thereof without carriage of substantial amounts away from the site to be treated, thereby accumulating an amount of the drug at the site to be treated for a prolonged period of time, then the use of the drug for example a non-steroidal anti-inflammatory drug at a site may have many other useful applications.

SUMMARY OF THE INVENTION

Applicants have now developed compositions, (combinations and formulations) which are topically applied to the skin and/or exposed tissue of a human and which are quickly transported in dosage amounts percutaneously (intracutaneously) at a site in need of treatment, (site of pathology and/or trauma) best targeting the epidermis and subsequently remaining (accumulating) at the site for a prolonged period of time. The compositions subsequently clear through the lymphatics thereby bringing dosage amounts of the compositions to the lymphatics for the treatment of disease and conditions in the lymphatics.

These compositions, (combinations and formulations) employ, combine, or incorporate (as the case may be) a plurality of effective non-toxic dosage amounts, each dosage amount comprising an effective non-toxic dosage amount of a drug for example a drug which inhibits prostaglandin synthesis for example an NSAID and an effective non-toxic dosage amount of a form of hyaluronic acid (preferably hyaluronic acid or salt thereof) for the transport of the drug to the site of the pathology and/or trauma. Suitable dosage amounts of the

composition may be removed from a container (for example a tube or jar) and administered (for example, applied).

In a first embodiment of this invention there is disclosed a pharmaceutical composition comprising a plurality of effective non-toxic dosage amounts of a composition, each such dosage amount comprising a therapeutically effective non-toxic dosage amount of a drug for the treatment of a disease or condition of the skin or exposed tissue at the site of the pathology or trauma and an effective non-toxic dosage amount of at least $5\text{mg}/\text{cm}^2$ of a form of hyaluronic acid selected from hyaluronic acid and salts thereof to transport the drug to the site of the pathology or trauma of the disease or condition, wherein the molecular weight of the form of hyaluronic acid is less than 750,000 Daltons and greater than 150,000 Daltons.

In a second embodiment of this invention there is provided a topically applicable percutaneous penetrating and best targeting the epidermis systemic independent acting pharmaceutical composition comprising a plurality of dosage amounts, each dosage amount comprising, a therapeutically effective non-toxic dosage amount to treat and to assist to resolve a disease or condition of the skin and exposed tissue, selected from at least one of the group consisting of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, malignancies or tumours of the skin primary and metastatic melanoma in the skin, genital warts, condyloma acuminata, cervical cancer, and Human Papilloma Virus including HPV of the cervix, psoriasis, both plaque-type psoriasis and nail bed psoriasis, corns on the feet and hair loss on the head of pregnant women, non-toxic to the patient dosage amount of a non-steroidal anti-inflammatory drug (NSAID) selected from the group consisting of diclofenac, diclofenac sodium, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac and an effective non-toxic amount of at least $5\text{ gm}/\text{cm}^2$ of the skin or tissue to which the effective dosage amount is to be applied, of a form of hyaluronic acid selected from hyaluronic acid and pharmaceutically acceptable salts thereof to facilitate the non-steroidal anti-inflammatory drug's rapid transport by the form of the hyaluronic acid to the site in the skin including the epidermis or exposed tissue of the disease or condition into the tissue to remain there for a prolonged period of time to assist to treat and assist to resolve the disease or condition by blocking prostaglandin synthesis wherein the percentage of the composition of the form of hyaluronic acid is about 2-1/2% by weight of the composition and has a molecular weight of between 150,000 Daltons and less than 750,000 Daltons and the non-steroidal anti-inflammatory agent is about 3% by weight of the composition.

In a third embodiment of this invention there is provided a pharmaceutical composition comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat disease or condition of the skin or exposed tissue; and

(2) a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof, characterized in that said composition is in such an amount and in such form that (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site of the skin or exposed tissue to be treated, and (ii) component (2) is immediately available to transport (facilitate or cause the transport of) component (1) to the site of trauma or pathology of the disease or condition to be treated, percutaneously into the skin or exposed tissue where the composition resides and accumulates for a prolonged period, and which component (2) is in an effective non-toxic dosage amount of at least 5mg/cm² of the skin or exposed tissue to transport component (1) upon administration, percutaneously into the skin or exposed tissue to the site of the trauma or pathology.

In a fourth embodiment of this invention there is provided a composition from which effective dosage amounts may be taken and applied to human skin or exposed tissue suffering pain, the composition comprising a plurality of dosage amounts which may be taken and applied, each dosage amount comprising an effective non-toxic dosage amount of a non-steroidal anti-inflammatory drug (NSAID) and an effective non-toxic dosage amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof hyaluronic acid exceeding 10 mg. per square cm (cm²) of skin or exposed tissue to which it is applied, for percutaneous transport of the NSAID by the form of hyaluronic acid into the epidermis proximate the paccinian nerve bundles to abate the pain.

In a fifth embodiment of this invention there is provided a dosage amount of pharmaceutical composition comprising: 5% by weight glycerine, 3% by weight benzyl alcohol, 3% by weight diclofenac sodium, 2.5% by weight sodium hyaluronate having a molecular weight greater than 150,000 daltons and less than 750,000 daltons, and sterile water in a container.

In a sixth embodiment of this invention there is provided a dosage amount of pharmaceutical composition suitable for topical application comprising 20% by weight methoxypolyethylene glycol, 1% by weight benzyl alcohol, 3% by weight diclofenac sodium, 2.5% by weight sodium hyaluronate having a molecular weight greater than 150,000 daltons and less than 750,000 daltons, and sterile water in a container.

In a seventh embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 3% by weight of the composition of glycerine, 1.5% by weight of the composition of benzyl alcohol, 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 Daltons, 3% by weight of the composition of liquid wax and sterile water, characterized in that the said pharmaceutical composition is 1500 gm, said composition is in a dosage form and said pharmaceutical composition comprises a

plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation in the epidermis before passage therefrom.

In an eighth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 5% of weight of the composition of glycerine, 3% by weight of the composition of benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 Daltons and sterile water, characterized in that the said pharmaceutical composition is 3000 gm, said composition is in a dosage form and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a ninth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 20% by weight of the composition of methoxypolyethylene glycol, 1% by weight of the composition of benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 Daltons and sterile water, characterized in that the said pharmaceutical composition is 1600 gm, said composition is in a dosage form and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a tenth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 20% by weight of the composition of a solubilizer, methoxypolyethylene glycol, 1% by weight of the composition of a preservative, benzyl alcohol, 3% by weight of the composition of diclofenac sodium,

2.5% by weight of the composition of sodium hyaluronate having molecular weight of 679,000 Daltons and sterile water, characterized in that the said pharmaceutical composition is 1600 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In an eleventh embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 5.5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen, 1% by weight of the composition of benzyl alcohol, 1% by weight of the composition of glycerin, 3% by weight of the composition of sodium hyaluronate, having a molecular weight of 661,600 Daltons and sterile water, characterized in that the said pharmaceutical composition is 227 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a twelfth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amount can be taken comprising: 4% by weight of the composition of meglumine, 2% by weight of the composition of piroxicam, 2.5% by weight of the composition of sodium hyaluronate, having a molecular weight of 661,600 Daltons and sterile water, characterized in that the said pharmaceutical composition is 217 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a thirteenth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: an oily phase comprising 15% by weight of the

composition of a liquid wax, 16% by weight of the composition of a wax and 5% by weight of the composition of glycerin; and an aqueous phase comprising 5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen, 1.5% by weight of the composition of sodium hyaluronate having a molecular weight of 200,000 Daltons and 0.3% by weight of the composition of a preservative, suttocide A and sterile water, characterized in that the said pharmaceutical composition is 3384 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a fourteenth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 3% by weight of the composition of glycerin, 1.5% by weight of the composition of benzyl alcohol, 3% by weight of the composition of liquid wax, 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 Daltons and sterile water, characterized in that the said pharmaceutical composition is 3100 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a fifteenth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 1.5% by weight of the composition of a preservative, benzyl alcohol, 3% by weight of the composition of glycerin, about 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of liquid wax, 3% by weight of the composition of sodium hyaluronate having a molecular weight is 661,600 Daltons, and sterile water characterized in that the said pharmaceutical composition is about 1550 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on

application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a sixteenth embodiment of this invention there is provided a multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: an oily phase comprising 15% by weight of the composition of a liquid wax, 16% by weight of the composition of a wax and 5% by weight of the composition of glycerine; and an aqueous phase comprising 5% by weight of the composition of meglumine, 1.5% by weight of the composition of sodium hyaluronate having a molecular weight 207,000 Daltons, 5% by weight of the composition of ibuprofen and a 0.3% by weight of the composition of a preservative, 10 sutocide and sterile water, characterized in that the said pharmaceutical composition is 3385 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is 15 to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In a seventeenth embodiment of this invention there is provided a multidose 20 multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 2.5% by weight of the composition of sodium hyaluronate having a molecular weight is 661,600 Daltons, 1% by weight of the composition of flunixin meglumine and sterile water, characterized in that the said pharmaceutical composition is 3000 gm, said composition is in a dosage form and 25 comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed 30 tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

In an eighteenth embodiment of this invention there is provided a method of treating a disease or condition of the skin or exposed tissue comprising administering topically a non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable 35 for topical application, a therapeutically effective non-toxic dosage amount of a drug which inhibits prostaglandin synthesis, and an effective non-toxic dosage amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof to transport the drug into the skin or exposed tissue at the site of the disease or condition to be treated 40 percutaneously into epidermis by rubbing the composition into the skin or exposed tissue

and wherein the concentration of the drug is 1-5% by weight and the concentration of the form of hyaluronic acid is 1-3% by weight of the composition.

In a nineteenth embodiment of this invention there is provided a method of percutaneous delivery of a therapeutically effective dosage amount of a drug which inhibits prostaglandin synthesis in a pharmaceutical composition the drug being transported to the site of trauma or pathology of the skin or exposed tissue of a human to treat a disease or condition of the skin or exposed tissue the delivery comprising topically administering to the skin or exposed tissue, the therapeutically effective non-toxic dosage amount of the drug which inhibits prostaglandin synthesis, in a composition which comprises an effective non-toxic amount of hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons sufficient to transport the drug to the epidermis of the skin to the site of the trauma or pathology to block the synthesis of prostaglandins and wherein the concentration of the drug is 1-5% by weight and the concentration of the form of hyaluronic acid is 1-3% by weight of the composition.

In a twentieth embodiment of this invention there is provided a method of treating a disease or condition selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus (HPV), Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated.

In a twenty first embodiment of this invention there is provided a method of treating pain topically, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat pain of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of pain to be treated, in the skin or exposed tissue.

10 In a twenty second embodiment of this invention there is provided percutaneous delivery of a therapeutically effective dosage amount of a drug which inhibits prostaglandin synthesis said dosage amount taken from a pharmaceutical composition and applied to the skin or exposed tissue of a human, the drug being transported to the site of trauma or pathology, on or in the skin or exposed tissue of the human, to treat a disease
15 or condition of the skin or exposed tissue, the delivery comprising topically administering to the skin or exposed tissue site of the trauma or pathology the therapeutically effective non-toxic dosage amount of the drug which inhibits prostaglandin synthesis in a composition which also comprises an effective non-toxic amount of hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than
20 750,000 daltons sufficient to transport the drug to the epidermis to the site of the trauma or pathology to block the synthesis of prostaglandin, wherein the amount of hyaluronic acid or salts thereof exceeds at least about 5mg/cm² of the skin or exposed tissue to which the composition is to be applied and wherein the concentration of the drug is 1-5% by weight and the concentration of the form of hyaluronic acid is 1-3% by weight of the
25 composition.

In a twenty third embodiment of this invention there is provided a method of treating a disease or condition selected from the group consisting of actinic keratoses, liver spots, squamous cell tumours, malignancies of the skin, genital warts, cervical cancer, Psoriasis, corns on the feet, and hair loss on the head of pregnant women, said
30 method comprising administering topically to the skin or exposed tissue of a human a dosage amount of a pharmaceutical composition, said dosage amount consisting essentially of:

(1) an agent selected from a medicinal and therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed
35 tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof.

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage
40 amount is to be applied, and is in such for that component (2) is immediately available to

transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated and wherein the form of hyaluronic acid has a molecular weight less than 750,000 Daltons and greater than 150,000 Daltons, said administrations continuing until such time as no longer
5 required and wherein component (2) is between about 1% and about 3% by weight of the composition and wherein component (1) is between 1% and about 5% by weight of the composition.

In a twenty fourth embodiment of this invention there is provided a method of treating pain topically, said method comprising administering topically to the skin or
10 exposed tissue of a human a dosage amount of a pharmaceutical composition, said dosage amount comprising:

- (1) a non-steroidal anti-inflammatory drug (NSAID) in a therapeutically effective amount to treat pain of the skin or exposed tissue and;
- (2) a form of hyaluronic acid selected from the group consisting of hyaluronic
15 acid, its non-toxic salts and combination thereof being between 1% and 3% by weight of the composition.

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the
20 dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of pain to be treated, in the skin or exposed tissue, and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 Daltons.

25 In a twenty fifth embodiment of this invention there is provided a method of treating a mammal for a condition of the skin or exposed tissue selected from the group consisting of basal cell carcinoma and actinic keratoses, which method consists essentially of topically administering to the site of the condition, more than once per day over a period of days sufficient to treat the condition, a non-toxic effective dosage amount of a
30 composition consisting essentially of

- (a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis,
- (b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site
35 of the condition, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and 750,000 daltons, and
- (c) a pharmaceutical excipient suitable for topical application.

In a twenty sixth embodiment of this invention there is provided a method of treating a mammal for a condition of the skin or exposed tissue selected from the group consisting of basal cell carcinoma and actinic keratoses, which method consists essentially of topically administering to the site of the condition, more than once per day over a
 5 period of days sufficient to treat the condition, a non-toxic effective dosage amount of a composition consisting essentially of

- (a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis, wherein the concentration of the NSAID between 1-5% by weight of the composition,
- 10 (b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site of the condition, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and
 15 750,000 daltons, and
- (c) a pharmaceutical excipient suitable for topical application.

In a twenty seventh embodiment of this invention there is provided a method of treating a mammal for actinic keratosis of the skin or exposed tissue, which method consists essentially of topically administering to the site of the actinic keratosis, more than
 20 once per day over a period of days sufficient to treat the actinic keratosis, a non-toxic effective dosage amount of a composition consisting essentially of

- (a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis,
- 25 (b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site of the actinic keratosis, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and 750,000 daltons, and
- 30 (c) a pharmaceutical excipient suitable for topical application.

In a twenty eighth embodiment of this invention there is disclosed a pharmaceutical composition from which effective non-toxic dosage amounts may be taken and applied to the skin or exposed tissue of a human, each effective dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage
 35 amount of a non-steroidal anti-inflammatory drug to treat a disease or condition of the skin or exposed tissue of a human involving a pathology and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof sufficient to transport the drug percutaneously into the skin or exposed tissue to accumulate and remain in the epidermis
 40 for a prolonged period of time and which is systemic independent acting and wherein said

pharmaceutical composition comprises 3% by weight of the drug and 2.5% by weight of the form of hyaluronic acid having a molecular weight less than 750,000 daltons and greater than 150,000 daltons.

In a twenty ninth embodiment of this invention there is disclosed a dosage amount of a pharmaceutical composition comprising:

- (1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue involving a pathology; and
- (2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof and combination thereof having a molecular weight less than 750,000 daltons and greater than 150,000 daltons,

characterized in that the dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and in a form immediately available to transport component (1) percutaneously into the epidermis of skin or exposed tissue to the site of trauma or pathology of the disease in the skin or exposed tissue to be treated on application to the skin or exposed tissue for accumulation in the epidermis before passage therefrom and wherein the concentration by weight of component (1) and the concentration by weight of component (2) are selected from one of the group consisting of:

- (i) the concentration of component (2) equals 2.5% by weight of the dosage amount and component (1) is a non-steroidal anti-inflammatory drug (NSAID);
- (ii) component (2) equals or is less than 3% by weight of the dosage amount but equals or exceeds 1% by weight and component (1) equals or exceeds 1% by weight of the dosage amount but is less than 5% by weight.

In a thirtieth embodiment of this invention there is disclosed a dosage amount of pharmaceutical composition suitable for controlling the unloading of a drug from the skin or exposed tissue of a human into the lymphatic system, the dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat disease in the lymphatic system in human and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and salts thereof and combination thereof sufficient to control the unloading of the drug into the lymphatic system wherein the effective amount of the form of hyaluronic acid exceeds 5 mg/cm² of the skin or exposed tissue and the molecular weight of the form of hyaluronic acid is greater than 150,000 Daltons and less than 750,000 Daltons and wherein the form of hyaluronic acid present is between 1% to 3% by weight of the dosage amount.

In a thirty first embodiment of this invention there is disclosed a dosage amount of pharmaceutical composition suitable for application to the skin or exposed tissue of a human, the dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic amount of a non-steroidal anti-inflammatory drug

(NSAID) to treat pain of the skin and exposed tissue of a human and an effective non-toxic amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and salts thereof and combinations thereof sufficient to transport and facilitate the drug percutaneously into the epidermis of the skin or exposed tissue of the

5 pain to be treated wherein the dosage amount of the composition accumulates and remains in the epidermis for a prolonged period of time and which is systemic independent acting and wherein the effective amount of the form of hyaluronic acid exceeds 10 mg/cm^2 of the skin or exposed tissue and the molecular weight of the form of hyaluronic acid is greater than 150,000 Daltons and less than 750,000 Daltons.

10 In a thirty second embodiment of this invention there is disclosed a dosage amount of a pharmaceutical composition comprising:

(1) a therapeutically effective amount of a drug to treat a disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic

15 acid, salts thereof and combinations thereof having a molecular weight greater than 150,000 Daltons and less than 750,000 Daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue in which component (2) exceeds 10 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be

20 applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom, and wherein the concentrations by weight of

25 components (1) and (2) in the dosage amount are selected from the group consisting of:

(xii) component (2) equals 2.5% by weight of the dosage amount and component (1) equals 3% by weight of the dosage amount, and

(xiii) component (2) equals or is less than 3% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount and component (1) equals

30 or is less than 5% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount.

In a thirty third embodiment of this invention there is disclosed the dosage amount of Claim 38 or 39 wherein the form of hyaluronic acid is sodium hyaluronate and wherein the drug is diclofenac or salts thereof.

35 In a thirty fourth embodiment of this invention there is disclosed a pharmaceutical composition from which an effective non-toxic dosage amounts are to be taken and applied topically to the skin or exposed tissue of a human, each effective dosage amount consisting essentially of pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat diseases and conditions of the skin or

40 exposed tissue of a human and an effective non-toxic dosage amount of a form of

hyaluronic acid selected from the group consisting of hyaluronic acid, non-toxic salts thereof and combination thereof having a molecular weight less than 750,000 daltons and greater than 150,000 daltons sufficient to transport the drug percutaneously into the epidermis of the skin or exposed tissue of a site in need of treatment wherein the composition accumulates and remains in the epidermis for a prolonged period of time and which is systemic independent acting and wherein the drug in the pharmaceutical composition is between about 1% and about 5% by weight of the composition and the amount of the form of hyaluronic acid in the composition is between about 1% and about 3% by weight of the composition and wherein each dosage to be taken comprises a minimum of 5 mg of the form of hyaluronic acid per square centimeter of skin or exposed tissue to which it is to be applied.

In an thirty fifth embodiment of this invention there is disclosed a composition comprising in a form suitable for administration to the skin or exposed tissue of a human comprising: an effective amount of a non-steroidal anti-inflammatory agent (NSAID) being between about 1% and about 5% of the composition by weight, an amount of hyaluronic acid or salts thereof being between about 1% and about 3% by weight of the composition, a preservative and a solubilizer if required and water, the composition being such that an effective dosage amount may be taken from the container and applied to the skin or exposed tissue wherein the hyaluronic acid or salts thereof rapidly transports the drug to a site of trauma or pathology in the skin or tissue to which the composition is applied and which accumulates there and remains there for a prolonged period of time and which composition is systemic independent acting.

In a thirty sixth embodiment of this invention there is disclosed a composition comprising in gel or cream form suitable for topical application, 3% by weight diclofenac, 2 1/2% by weight hyaluronic acid or a salt thereof having a molecular weight less than about 750,000 Daltons and greater than 150,000 Daltons, a solubilizer for solubilizing the diclofenac, and a preservative.

In a thirty seventh embodiment of this invention there is disclosed a dosage amount of a pharmaceutical composition consisting essentially of

- (1) pharmaceutical excipients suitable for topical application including water;
- (2) a therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and exposed tissue and;

(3) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-toxic salts thereof, having a molecular weight less than 750,000 daltons and greater than 150,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and exposed tissue, is in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (3) is immediately available to transport component (2) percutaneously into the epidermis of the skin or exposed tissue

to the site of trauma and pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom, and wherein the concentrations by weight of components (2) and (3) in the dosage amount are selected
5 from:

- (i) component (3) equals or is less than 3% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount and component (2) equals or is less than 5% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount, and
- 10 (ii) component (3) is about 2 1/2% by weight of the dosage amount and component (2) is 3% by weight of the dosage amount.

In an thirty eighth embodiment of this invention there is disclosed a method of treating a disease or condition in humans, the method comprising topically administering a pharmaceutical composition from which effective non-toxic dosage amounts may be
15 taken and applied to the skin or exposed tissue of a human, each effective dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat the disease or condition of the skin or exposed tissue of a human and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and
20 combination thereof sufficient to transport the drug, to a site in the skin including epidermis or exposed tissue of the disease or condition for percutaneous transport into the skin or exposed tissue to accumulate and remain there for a prolonged period of time and which is systemic independent acting and wherein the concentration of the drug is 3% by weight and the concentration of the form of hyaluronic acid is 2.5% by weight having a
25 molecular weight less than 750,000 daltons and greater than 150,000 daltons and wherein the dosage amount of the form of hyaluronic acid exceeds 5mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied.

In a thirty ninth embodiment of this invention there is disclosed a method of treating a disease or condition selected from the group consisting of basal cell carcinoma, actinic
30 keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus, Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said
35 dosage amount comprising:

- (1) a medicinal or therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed tissue and;
- (2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds $5\text{mg}/\text{cm}^2$ of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, wherein the concentration of component (1) is between 1% and 5% by weight of the composition and the concentration of component (2) is between 1% and 3% having a molecular weight less than 750,000 daltons and greater than 150,000 daltons.

In a fortieth embodiment of this invention there is disclosed a method of treating actinic keratoses, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

- (1) a medicinal or therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed tissue and;
- (2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-toxic salts thereof, and combination thereof having a molecular weight in the range of 150,000 to 750,000 daltons,

said dosage amount of said composition is in a dosage form suitable for topical application to the skin and/or exposed tissue and in a dosage amount in which component (2) exceeds $5\text{ mg}/\text{cm}^2$ of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

In a forty first embodiment of this invention there is disclosed a method of rapidly transporting a drug to the epidermis and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective non-toxic dosage amount of a drug to treat a disease or condition of the skin or exposed tissue and an amount exceeding $5\text{mg}/\text{cm}^2$ of the skin or exposed tissue of hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons to facilitate the rapid transport of the drug to the site in the skin or tissue of the disease or condition to the site of the pathology or trauma to accumulate there and be retained there for a prolonged period of time.

In a forty second embodiment of this invention there is disclosed a method of accumulating a drug in the skin or exposed tissue of a human suffering from trauma or a pathology comprising topically administering to the skin or exposed tissue a composition comprising the drug and an effective non-toxic amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons comprising hyaluronic acid and non-toxic salts thereof to transport the drug into the skin or exposed tissue wherein the amount of the form of hyaluronic acid exceeds at least about 5 mg/cm² of the surface area of the skin or exposed tissue to which the composition is applied.

10 In a forty third embodiment of this invention there is disclosed a method of treating a disease or condition selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus, Psoriasis, corns on the feet, hair loss on the head of pregnant
15 women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue and;

20 (2) a form of hyaluronic acid selected from hyaluronic acid and non-toxic salts thereof,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage
25 amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom wherein component (1) is between 1%
30 and 5% by weight of the composition and component (2) is between 1% and 5% weight of the composition and has a molecular weight less than 750,000 daltons and greater than 150,000 Daltons.

In a forty fourth embodiment of this invention there is disclosed a method of accumulating a drug and a form of hyaluronic acid in the skin or exposed tissue or both
35 comprising topically administering a dosage of a pharmaceutical composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective to treat and resolve a disease or condition of the skin and exposed tissue, selected from the group consisting of basal cell carcinoma and actinic keratoses, and pain non-toxic to the patient amount of a drug and an effective non-toxic dosage amount of a
40 form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-

toxic salts thereof sufficient to facilitate the drug's quick penetration to the site in the skin or tissue of the disease or condition to accumulate and remain there for a prolonged period of time wherein the percentage of the dosage of the form of the hyaluronic acid is between 1% and 3% by weight of the dosage and has a molecular weight less than 750,000 Daltons and greater than 150,000 daltons and the percent of the drug of the composition is between 1% and 5% by weight of the dosage.

In a forty fifth embodiment of this invention there is disclosed a method of quickly delivering a drug to the epidermis and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a dosage of a pharmaceutical composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective, to treat and resolve a disease a condition of the skin and exposed tissue, selected from the group consisting of basal cell carcinoma and actinic keratoses, non-toxic to the patient amount of a drug which blocks prostaglandin synthesis and an amount of a form of hyaluronic acid selected from hyaluronic acid non-toxic salts thereof sufficient to facilitate the drug's quick penetration to the site in the skin or tissue of the disease or condition through the tissue to accumulate and remain there for an prolonged period of time to block prostaglandin synthesis wherein the percentage of the dosage of the form of the hyaluronic acid is between 1% and 3% by weight of the dosage and has a molecular weight less than 750,000 daltons and greater than 150,000 daltons and the percent of the drug of the composition is between 1% and 5% by weight of the dosage.

In a forty sixth embodiment of this invention there is disclosed a method of treating pain topically, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a non-steroidal anti-inflammatory drug (NSAID) in a therapeutically effective amount to treat pain of the skin or exposed tissue and;

(2) hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of pain to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

In a forty seventh embodiment of this invention there is disclosed a method of accumulating a medicine or therapeutic agent (component (1)) and a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000

daltons (component (2)) in the epidermis of the skin or exposed tissue of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a pharmaceutical composition comprising components (1) and (2) characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, and wherein the pharmaceutical composition further comprising pharmaceutical excipients suitable for topical application.

In a forty eighth embodiment of this invention there is disclosed a method of rapidly transporting a drug to the epidermis and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective non-toxic dosage amount of a drug to treat a disease or condition of the skin or exposed tissue at the site the trauma or pathology, and an amount of hyaluronic acid or salts thereof to facilitate the rapid transport of the drug to the site in the skin or tissue of the disease or condition to accumulate there and be retained there for a prolonged period of time and wherein the form of hyaluronic acid is administered in excess of 5 mg/cm² having a molecular weight greater than 150,000 daltons and less than 750,000 daltons.

In a forty ninth embodiment of this invention there is disclosed a method of controlling the unloading of a drug from the skin or exposed tissue of a human suffering trauma or pathology into the lymphatic system comprising: delivering an amount of drug into the skin or exposed tissue by an effective non-toxic dosage amount of a form of hyaluronic acid selected from units of hyaluronic acid and salts thereof to the skin or exposed tissue wherein the amount of a form of hyaluronic acid exceeds at least about 5 mg/cm² having a molecular weight greater than 750,000 Daltons and less than 150,000 Daltons.

In a fiftieth embodiment of this invention there is disclosed a method of accumulating a drug and a form of hyaluronic acid in the skin of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable for topical applications, an effective non-toxic dosage amount of a drug which inhibits prostaglandin synthesis to treat a disease or condition of the skin involving pathological tissue or underperfused tissue and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof effective to transport the drug percutaneously to the site in the epidermis of the

skin of the disease or condition to accumulate and remain at the site in the skin or exposed tissue for a prolonged period of time before passage therefrom, wherein the amount of the form of hyaluronic acid administered is at least 5 mg/cm^2 of skin having a molecular weight of less than 750,000 daltons and greater than 150,000 daltons.

5 In a fifty first embodiment of this invention there is disclosed a method of accumulating a medicine or therapeutic agent which inhibits prostaglandin synthesis (component (1)) and a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and combination thereof, having a molecular weight of less than 750,000 daltons and greater than 150,000 daltons (component (2)) in the epidermis
10 of the skin of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a pharmaceutical composition comprising components (1) and (2) characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin to which the dosage amount is to be applied, and is in such form
15 that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin to the site of trauma or pathology of the disease or condition to be treated in the skin, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, and wherein the pharmaceutical composition further comprises pharmaceutical excipients suitable for
20 topical application.

In a fifty second embodiment of this invention there is disclosed a method of accumulating a drug in the skin or exposed tissue of a human suffering from trauma or a pathology comprising topically administering to the skin or exposed tissue a composition comprising the drug which inhibits prostaglandin synthesis and an effective non-toxic
25 amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and combination thereof, having a molecular weight of less than 750,000 daltons and greater than 150,000 daltons to transport the drug into the skin wherein the amount of the form of hyaluronic acid exceeds at least about 10 mg/cm^2 of the surface area of the skin to which the composition is applied.

Furthermore, application of the dosage amounts of the compositions, combinations and formulations are, systemic independent (there is a lack of a blood level of the drug for example NSAID), are quick to penetrate into the skin to the site of the trauma and/or pathology because the effective dosage amount of the form of hyaluronic acid transports (facilitates or causes the transport of) the drug (for example NSAID) particularly to the epidermis where the composition, combination or formulation accumulates and remains for prolonged periods. The compositions subsequently clear through the lymphatics and are available for the treatment of disease and conditions of the lymphatics.

In this regard effective amounts of the form of hyaluronic acid exceeds in the order of about 5 mg per square cm. (cm²) of the area of for example the skin and/or exposed tissue to which the dosage amounts of the composition is to be applied.

Thus, according to another aspect of the invention, Applicants have provided topically applicable percutaneous (intracutaneous) penetrating (best targeting the epidermis) systemic independent acting (not acting essentially through the blood) pharmaceutical compositions (combinations and formulations) comprising a plurality of dosage amounts each comprising, together with pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and to assist to resolve diseases and conditions of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin primary and metastatic melanoma in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example,

exceeds about 5-10 mg per square centimeter (cm²) of skin and/or exposed tissue to which it is to be applied.

According to another aspect of the invention there is provided the use of:

5 (1) a medicinal and/or therapeutic agent for example which inhibits prostaglandin synthesis,

and (2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid,

10 in the manufacture of a pharmaceutical composition for treating a disease or a condition (for example those discussed above) of the skin and/or exposed tissue in therapy wherein dosage amounts taken from the composition each comprise:

15 (1) a therapeutically effective amount of said medicinal and/or therapeutic agent and

(2) a therapeutically effective amount of the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid, the pharmaceutical composition being characterized in that for each dosage amount taken from the pharmaceutical composition, the amount of component (2) is immediately available to transport component (1) percutaneously to the site of trauma and/or pathology for example into the epidermis where the composition accumulates

25 and remains for a prolonged period, at the site of the skin or exposed tissue to be treated, and component (2) is in an effective non-toxic amount to transport (facilitate or cause the transport of) component (1) into the skin or exposed tissue (for example into the epidermis). Preferably component (2) is hyaluronic acid and/or salts thereof and preferably the dosage amount of component (2) in the amount of the composition taken from the composition (to be taken from the composition) and applied to the skin or exposed tissue is a dose amount greater than about 5-10 mg per cm² of skin and/or exposed tissue to which the dosage amount is to be applied.

The pharmaceutical composition will normally include pharmaceutically compatible excipients to provide a form for ease of administration to the skin and/or exposed tissue for

transport into the epidermis. For example a suitable dosage amount of a gel may be squeezed from a tube as a ribbon of gel "X" cm long (which dosage amount (in the form of the ribbon "X" cm long) contains the effective non-toxic dosage amounts of the drug and form of hyaluronic acid. Or a dosage amount of cream packaged in a jar may be scooped from the jar by a measuring device or by "two fingers" in a suitable amount (for example in a spoon containing a premeasured volume or an amount about half the "length of the fingers"). Each of the dosage amounts selected comprises the effective amounts of drug (for example NSAID) and effective amount of the form of hyaluronic acid (for example hyaluronic acid and/or salts thereof). In this way the patient may "squeeze" or "scoop" or "what have you" the appropriate dosage amount and apply (rub in) the dosage amount onto the skin and/or exposed tissue for transport into the epidermis.

Thus, according to another aspect of the invention, a method of treating a disease and/or condition of the skin or exposed tissue, for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours in the skin, genital warts (condyloma acuminata), cervical cancer, HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women, in a human is provided comprising administering topically to human skin and/or exposed tissue an effective non-toxic dosage amount of a composition comprising, together with pharmaceutical excipients suitable for topical application to the skin and/or exposed tissue, for example in the form of a gel or cream (to give the composition definition and form so that specific dosage amounts are easily selected or taken for administration (for example squeezed from a tube or scooped from a jar and rubbed into the skin or exposed tissue), a therapeutically effective (to treat and to assist to resolve the disease or condition for example basal cell carcinoma or

other lesion), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, for example a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) to transport (facilitate or cause the transport of) the drug (for example NSAID) into the skin or exposed tissue to the site of the disease or condition to be treated percutaneously, (to the site of trauma and/or pathology), for example into the epidermis, where the form of hyaluronic acid and medicine accumulates and remains for a prolonged period of time thereby for example blocking prostaglandin synthesis in the skin or exposed tissue. The form of hyaluronic acid is then cleared through the lymphatics (lymphatics system).

Thus, according to another aspect of the invention, the treatment may employ the use of the composition, formulation or combination for the treatment of the diseases and conditions aforesaid as for example by applying dosage amounts of the composition, formulation or combination number of times daily (for example, 3 times daily) for a period of time, for example, 2-4 weeks to clear the disease, lesion or condition. Each dosage amount applied will depend upon the size of the lesion or condition on the skin or exposed tissue. For example, a suitable dosage amount may include 5-10 mg. of the form of hyaluronic acid per 1 cm² skin area or exposed tissue area.

One such formulation may comprise 3% (by weight) diclofenac in a 2 1/2% (by weight) hyaluronic acid (sodium hyaluronate - molecular weight 661,600) gel formulation, with the excipients being glycerine (5%), benzyl alcohol (3%) (acting in part as a solubilizer and preservative), and sterile water (the balance) in a 50 gm. tube of the composition (a plurality of dosage amounts) whose tube O.D. (outer diameter) of the opening through which the gel

formulation is discharged from the tube is 8 mm and whose I.D. (inner diameter) of the opening is 4 mm. Therefore a ribbon 2-3 cm in length, squeezed from a tube gives about 5 mg-7 1/2 mg of hyaluronic acid for application to a skin or exposed tissue surface area of 1-1 1/2 cm² with an effective dosage amount of diclofenac. While greater amounts squeezed from the tube, may be applied, the application of substantial excessive dosage amounts to the skin and/or exposed tissue may saturate the skin or exposed tissue and thus the epidermis. (There is therefore no more room for the composition to pass between the cells and therefore further applications at that time will not provide additional benefit). Where pain relief is also required additional dosage amounts, for example in excess of about 10 mg. of the hyaluronic acid taken from the same pharmaceutical composition applied per/cm² of surface area of the skin or exposed tissue may be required to be applied.

Another formulation may comprise 3% (by weight) diclofenac in a 2 1/2% (by weight) hyaluronic acid (sodium hyaluronate - molecular weight 675,000) gel formulation (also in a tube) with excipients being benzyl alcohol (1%) (a preservative), methoxypolyethylene glycol 350 (20% by weight) (a solubilizer), and sterile water (the balance).

While the above compositions, combinations and formulations are proposed, provided there is sufficient amounts of the form of the hyaluronic acid (for example, sodium hyaluronate) in the dosage amounts applied to the skin and/or exposed tissue to facilitate or cause the percutaneous (intracutaneous) transport of the drug for example which inhibits prostaglandin synthesis, preferably an NSAID (for example, diclofenac) to block prostaglandin synthesis, then the formulations may be of any suitable form, for example, a 1% lotion of hyaluronic acid with NSAID, or a cream or gel or any other suitable form.

Therefore according to another aspect of the invention, there is provided containers (for example tubes and jars) containing compositions comprising a plurality of dosage amounts of the drug and form of hyaluronic acid, each dosage amount comprising an effective non-toxic dosage amount of the drug and an effective non-toxic dosage amount of the form of

this reason was considered appropriate to be used in human conditions. Thus, Indocid™ solubilized in NMG may be administered with hyaluronic acid topically for percutaneous penetration at, for example, varying doses. The solution of indomethacin and NMG may be mixed with, for example, "LifeCore™" hyaluronic acid in dosage amounts discussed above. This produces an appropriate mixture and can be administered safely.

When the NSAID, for example indomethacin (dissolved in n-methyl glucamine) or other NSAID, is applied topically in an effective dosage amount from a composition or formulation also including the effective dosage amount of the form hyaluronic acid, no major toxic side effects occur, such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of indomethacin (if necessary). (This may be in part because of the clearing of the hyaluronic acid through the lymphatic system from the site). In addition, the responses that have been observed are dramatic when the drug for example NSAID (for example diclofenac) is combined with hyaluronic acid, demonstrating clearly that the combination is now "targeting" to the site of pathology or trauma, or pathological tissue. Furthermore, patients using the formulations and combinations of drug (for example NSAID) - hyaluronic acid (sodium hyaluronate) (for example, diclofenac or indomethacin and hyaluronic acid) experience dramatic relief of pain immediately.

Thus, Applicants believe that the use of the NSAID, for example with hyaluronic acid (sodium hyaluronate), deblocks the macrophages (and N.K. cells (Natural Killer Cells) thought to be immature macrophages) by preventing enzymatic production of prostaglandin which blocks macrophage (and N.K. cell) functioning. The hyaluronic acid (and salt and other forms) not only enhances the activity of the drug (NSAID) but also reduces any side effects and toxicity that is associated with the use of the prostaglandin synthesis inhibitors. When effective dosage amounts of compositions, formulations and combinations containing effective dosage amounts of the drugs for example, (NSAIDs (for example, diclofenac)) and effective dosage amounts of, for example,

hyaluronic acid or the sodium salt thereof, are applied to for example the tumour lesion (for example basal cell carcinoma) or other condition (for example, actinic keratoses lesion) for a period of time (for example, 3 times daily for 2-4 weeks), the carcinoma and lesions, as the case may be, disappear.

Applicants also postulate that when the combination or formulation is applied to the disease or condition (for example, basal cell carcinoma or actinic keratoses), the hyaluronic acid passes between the cells (in the stratum corneum and epidermis to the dermis depending on amounts) to the areas of trauma and/or pathology deficient in hyaluronic acid (or forms thereof), transporting, taking, drawing, carrying or pulling the NSAID with it to the sites of prostaglandin synthesis, penetrating to inhibit prostaglandin synthesis until the space between the cells is saturated. The NSAID now being proximate the Paccinian nerve bundle (superficial nerve bundles at the end of the nerves) gives pain relief. The macrophages (which had been previously blocked) are unblocked and act to destroy the disease or condition for example basal cell carcinoma, actinic keratoses lesion, or other disease or lesion. Furthermore, the effective non-toxic dosage amount of the composition, combination or formulation, comprising the effective dosage amount of the form of hyaluronic acid and the effective dosage amount of NSAID passing through the stratum corneum to the epidermis and to the dermis (if a sufficient amount of the form of hyaluronic acid is present), passes into the skin, accumulating and staying longer in the skin at the site of the trauma and/or pathology. Therefore, after having had an immediate effect at the site of trauma and/or pathology (for example, relieving pain and acting on the basal cell carcinoma, actinic keratoses and other disease, condition or lesion), the NSAID-hyaluronic acid combination continues to accumulate at the site in need of treatment and thereafter clears through the lymphatic system.

Thus according to another aspect of Applicant's invention, Applicants' compositions, formulations and combinations quickly penetrate on application through the stratum corneum into the epidermis (to the dermis) by the form

of hyaluronic acid transporting the NSAID, to the site of trauma and/or pathology where the amounts applied accumulate and remain for a prolonged time for treatment.

15 Fifteen (15) minutes after application of one of Applicants' formulations, about three times the amount of Applicants' formulation has penetrated into the skin (particularly the epidermis) than formulations and combinations not containing hyaluronic acid or effective dosage amounts of hyaluronic acid, but containing the same 10 drug. Furthermore, the drug and hyaluronic acid accumulate and remain at the site in need of treatment for a longer period of time.

Thus according to another aspect of the invention, non-toxic effective dosage amounts of forms of hyaluronic acid 15 (preferably sodium hyaluronate) and effective non-toxic dosage amounts of a drug may be administered in compositions to sites of trauma or pathology, on/in the skin and/or exposed tissue (for example the epidermis) by the application of the effective non-toxic dosage amount of the composition 20 comprising an effective non-toxic dosage amount of a drug (for example an NSAID) and an effective non-toxic dosage amount of a form of hyaluronic acid (for example sodium hyaluronate) to the skin or exposed tissue whereby the forms hyaluronic acid transport the drug percutaneously to the site of trauma and/ 25 pathology, where the composition accumulates and remains for a prolonged period of time thereby retaining the drug at the site of trauma and/or pathology (for example the epidermis) for the treatment of the condition or disease and the reduction of pain.

30 Thus according to another aspect of the invention, Applicants have provided compositions (formulations and combinations) (including pharmaceutical excipients suitable for topical application) from which effective non-toxic (to the patient) dosage amounts of a drug (for example an NSAID) 35 to treat and to assist to resolve diseases and conditions of the skin and/or exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous

cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin, genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), and effective non-toxic dosage amounts of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to transport (to facilitate or cause the transport of) the drug, for example NSAID, are taken for application, to a site in the skin (for example epidermis) or exposed tissue having a disease or condition for percutaneous transport into the skin and/or exposed tissue to accumulate and remain there for a prolonged period of time to for example block prostaglandin synthesis. Thus an effective dosage amount of the composition or formulation or combination penetrates quickly into the skin, for example by the hyaluronic acid transporting the NSAID or causing the NSAID to be transported for example to the epidermis of the skin, accumulates there and remains there for a prolonged period of time, thereby accumulating the drug and forms of hyaluronic acid in the skin (particularly the epidermis).

Thus according to another aspect of the invention, a method of accumulating a drug and a form of hyaluronic acid in skin and/or exposed tissue is provided comprising topically administering a therapeutically effective non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable for topical applications, an effective non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) (to treat and to assist to resolve the disease and conditions of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions,

5 fungal lesions, "liver" spots and like lesions (found for the
most part in the epidermis), squamous cell tumours, metastatic
cancer of the breast to the skin, malignancies and/or tumours
of the skin, primary and metastatic melanoma in the skin,
10 genital warts cervical cancer, and HPV (Human Papilloma Virus)
including HPV of the cervix, psoriasis (both plaque-type
psoriasis and nail bed psoriasis), corns on the feet and hair
loss on the head of pregnant women), and an effective non-
toxic dosage amount of hyaluronic acid and/or salts thereof
15 (for example, the sodium salt) and/or homologues, analogues,
derivatives, complexes, esters, fragments, and/or sub-units of
hyaluronic acid (preferably hyaluronic acid and salts thereof
effective to transport (to facilitate or cause the transport
of) the drug (for example NSAID) percutaneously to the site in
the skin (for example epidermis) or exposed tissue of the
disease or condition to accumulate and remain there for a
prolonged period of time for example to block prostaglandin
synthesis.

20 According to another aspect of the invention, a
method of quickly delivering a drug to the skin or exposed
tissue, particularly the epidermis, and maintaining the drug
therein for a prolonged period of time is provided, the method
comprising topically administering (for example rubbing in)
an effective non-toxic dosage amount of a composition
25 comprising pharmaceutical excipients suitable for topical
application, a therapeutically effective (to treat and assist
to resolve the disease and/or condition of the skin and
exposed tissue (for example basal cell carcinoma, the
precancerous, often recurrent, actinic keratoses lesions,
30 fungal lesions, "liver" spots and like lesions (found for the
most part in the epidermis), squamous cell tumours, metastatic
cancer of the breast to the skin, primary and metastatic
melanoma in the skin, malignancies and/or tumours of the skin,
genital warts, cervical cancer, and HPV (Human Papilloma
35 Virus) including HPV of the cervix, psoriasis (both plaque-
type psoriasis and nail bed psoriasis), corns on the feet and
hair loss on the head of pregnant women)), non-toxic (to the
patient) dosage amount of a drug for example which inhibits
prostaglandin synthesis, preferably a non-steroidal anti-

inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to transport (to facilitate or cause the transport of) the drug for example the NSAID percutaneously to the site of the trauma and/or pathology in the skin (for example epidermis) or exposed tissue, for remaining there for a prolonged period of time (for example in the epidermis and dermis) to for example block prostaglandin synthesis. Suitable amounts of the form of hyaluronic acid may comprise in excess of 5 mg. per cm² in a form which transports the drug (for example molecular weights of the form of hyaluronic acid being less than about 750,000 Daltons or if at substantially greater molecular weights, diluted (to reduce) the concentration or autoclaved or cleaved if required to reduce the size of the molecules.

According to another aspect of the invention, a method of controlling the unloading of a drug from the skin or exposed tissue into the lymphatic system comprises delivering (transporting) an amount of drug into the skin or exposed tissue by an effective non-toxic dosage amount of a form of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid to the skin (epidermis) or exposed tissue to control the unloading of the drug into the lymphatic system (for example by the application of greater than 5 mg./cm²) of the form of hyaluronic acid.

Thus according to another aspect of the invention a composition is provided which when administered to a human by preferably administration to the skin and/or exposed tissue of a human, unloads its contents into the lymphatic system, the composition comprising an effective non-toxic dosage amount of a drug (for example an NSAID or an anti-cancer drug (Novantrone) and an effective non-toxic amount of hyaluronic acid and/or salts thereof and/or homologues, analogues,

derivatives, complexes, esters, fragments and/or sub-units of hyaluronic acid (for example at least about 5-10 mg/cm² of skin or exposed tissue). Thus the composition is made up of a plurality of such dosage forms (for example a cream or lotion or gel).

Thus according to another aspect of the invention, a new composition for treating diseases via the lymphatic system is provided comprising a plurality of effective non-toxic dosage amounts of the composition, each dosage amount comprising hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and/or sub-units of hyaluronic acid for passing into the lymphatic system and a therapeutic effective amount of medicine for treatment of a disease (which disease may be in the lymphatic system).

According to another aspect of the invention, the composition may be for application to the skin or exposed tissue.

According to another aspect of the invention, a composition is provided from which effective dosage amounts may be taken and administered, each effective dosage amount of the composition comprising an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, ester, fragments and/or sub-units for transporting a therapeutically effective non-toxic dosage amount of a medicine and/or therapeutic agent (for example an NSAID) in the composition into the skin and/or exposed tissue when applied thereto to an area of pathology and/or trauma then into the lymphatic system, the dosage amount being essentially systemic independent such that substantial amounts do not enter the blood system prior to clearing (passing) into the lymphatic system. Preferably the amount of the form of hyaluronic acid in each dosage amount administered is greater than about 5-10 mg./cm² and the molecular weight is less than about 750,000 daltons.

We have compared the penetration and retention of one of our combinations (formulations) with a control and Voltarol Emulgel in the skin as follows:

(A)

OUR FORMULATION

1% DICLOFENAC IN 3.0% HA GEL 50g/tube

EPDICLO1

LOT XPB 044

Quantity 1500ml

FORMULA	Supplier	Lot	Amount	Percent
10 Sterile Water	Baxter	AW45F1	1397ml	--
Glycerin	Life	1043	45g (36ml)	3%
Benzyl Alcohol	Caledon	02517	22.5g (22ml)	1.5%
Liquid Wax DICDD	Brooks	191-175	45g	3%
Diclofenac Sodium	Prosintex	9113003	15g	1%
15 Sodium Hyaluronate	Skymart	HG-1103	45g	3%
Mol. Wt. 661,600				

PROCEDURE

- 20 - Set up stirring apparatus using a 3 liter stainless steel beaker
- Add Water, Glycerin, Benzyl Alcohol and Liquid Wax DICDD, stir and mix for 10 minutes
- 25 - Add Diclofenac Sodium and stir for 30 minutes to dissolve
- Add Sodium Hyaluronate and stir for 90 minutes

FILLED

In a 50 ml aluminum collapsible tube,
inside of tube lacquered with a phenolic resin; outside
of tube white regular enamel coating;

5 9 mm white polypropylene screw on cap with pierce tip

Gels

Batch No.s

(B) Voltarol Emulgel

060400 10 93

(C) 1% Diclofenac Gel

XPB049 (Control)

10 (C)

CONTROL

1% DICLOFENAC IN CARAPOL GEL, 50g Jar

LOT XPB 049

Quantity 100ml

	<u>FORMULA</u>	<u>Supplier</u>	<u>Lot</u>	<u>Amount</u>	<u>Percent</u>
15	Sterile Water	Baxter	AW45N5	93ml	--
	Glycerin	BDH	2579	3g	3%
	Benzyl Alcohol	BDH	23797	1.5g	1.5%
	Liquid Wax DICDD	Brooks	1-1424	3g	3%
	Diclofenac Sodium	Prosintex	9113003	1g	1%
20	Carbopol 934	A&C Chemicals	910304	1g	1%

PROCEDURE

- Set up stirring apparatus using a 400ml stainless steel beaker

25 - Add Water, Glycerin, Benzyl Alcohol, Liquid Wax DICDD
and stir to mix thoroughly for 10 minutes

- Add Diclofenac Sodium and stir for 20 minutes to dissolve

30

- Very slowly add Carbopol 934, avoid getting lumps

Samples

Cell	Sample	Quantity of gel applied (mg)
5 A	060400 10 93	192
B	060400 10 93	192
C	EPDICLO1*	192
D	EPDICLO1*	192
E	XPB049	192
10 F	XPB049	192

* - Our Formulation

Skin Type

One piece of skin (Female, 37 years, smoker, breast skin) was used for one sample from each batch. A second piece of skin (no further details available) was used for the second sample from each batch. The skin was stored deep frozen (-20°C) until thawed for this experiment. Full thickness skin was used for this experiment.

Experimental Conditions

20 Skin permeation cells were prepared containing an exposed skin surface area of 9.6 cm^2 and a constantly stirred receptor fluid beneath the skin consisting of 135 ml of ethanol:phosphate buffered saline (25:75 v/v).

25 Each cell was allowed to equilibrate for 1 hour at 37°C after which the gel was spread evenly over the skin surface at a concentration of 20 mg/cm^2 . See table above. The cell was then maintained at 37°C with an air temperature above the skin of 35°C .

30 24 hours after application of the gel the experiment was stopped and a portion of the receptor fluid removed. The skin was removed from the cell and any gel remaining on the surface carefully wiped off with dry paper towel followed by paper towel moistened with water. The skin was cut with a scalpel to obtain thin top and thicker lower sections of skin.

35 This was done in order to obtain layers of skin which approximated the epidermal and dermal layers. Each skin section was weighed and the residual diclofenac extracted with 10ml of fresh receptor fluid using an ultra turrax

homogeniser. The homogenates were centrifuged and a portion of the resultant supernatant solutions removed.

The receptor fluid and skin extracts from each cell were assayed for diclofenac content by using a validated reverse phase high performance liquid chromatography (HPLC) method.

Results

Distribution of Diclofenac 24 hours after application of Diclofenac Gel

	Sample	Receptor	Top Skin portion			Bottom skin portion		
			µg	Skin Weight (g)	µg	µg/g	Skin Weight	µg
15								
	(Voltarol Emugel)							
20	060400 10 93	447	0.1363	101	742	1.2449	217	174
	060400 10 93	764	0.2445	141	577	1.2351	202	164
	Mean	606			660			169
25	(Our Formulation)							
	EPDICLO1	247	0.1535	13	867	1.4663	148	101
	EPDICLO1	292	0.1647	145	879	1.0022	86	86
30	Mean	269			873			93
	(Control)							
	XPB049	184	0.1275	35	272	1.1324	58	51
	XPB049	147	0.2068	82	396	1.0893	68	63
35	Mean	165			334			57

Thus having regard to the above and Figures 1', 2' and 3', it is clear that the sodium hyaluronate takes the diclofenac into the skin to the epidermis level (See Figure 1') more rapidly than the Voltarol Emugel or non-hyaluronic acid diclofenac containing control formulation, accumulates it there and retains it there longer. The other formulations permit the NSAID, diclofenac, to pass through the bottom skin portion (dermis) quicker, thereby clearing it from the epidermis and dermis, quicker. Furthermore, more of Applicants' formulation is in the epidermis and in the dermis even after 12 hours. With respect to Figure 1', the top of the graph should have the following heading "DICLOFENAC TOP SKIN PORTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS) (THOUSANDS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □ 0604001093 + EPDICLO1 ◇ XP8049". With respect to Figure 2', the top of the graph should have the following heading "DICLOFENAC BOTTOM SKIN PORTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □ 0604001093 + EPDICLO1 ◇ XP8049". With respect to Figure 3', the top of the graph should have the following heading "DICLOFENAC RECEPTOR SOLUTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □ 0604001093 + EPDICLO1 ◇ XP8049".

It is also clear that Applicants' formulations clear into the lymphatic system not through the blood system. Yet the prior art topical formulations have always tried "to drive" the formulations through the skin into the blood for treatment of the disease or condition in the area (i.e. systemic action).

Thus, our composition, formulation and combination, (and dosage amounts thereof) penetrate quickly and rapidly at the site of treatment through the upper skin into the epidermis, where the paccinian bundles are located and the NSAID and the form of hyaluronic acid are accumulated and are

retained longer, where needed (for example for the treatment of basal cell carcinoma).

Further, the NSAIDs are retained in the area to be treated with the form of hyaluronic acid. In doing so, they preclude prostaglandin synthesis, in effect, deactivating the synthesis or inhibiting the synthesis, of prostaglandins, permitting the macrophages' scavenger cell activity to eliminate the tumour and lesion. Additionally, a rapid onset of pain relief (analgesic effect) is provided (depending on the amount of NSAID and form of hyaluronic acid) usually where in excess of about 10 mg of the form of hyaluronic acid (preferably hyaluronic acid and salts thereof) is administered per cm² of surface area comprises the dosage amount administered. However, there are no blood levels of the NSAID in the immediate area of treatment. The forms of hyaluronic acid are thus cleared via the lymphatic system. Then the lymphatics pass the forms of hyaluronic acid, Applicants believe, to the blood system. Thus, the NSAIDs and forms of hyaluronic acid stay at the site to be treated for well in excess of 12 - 24 hours, a protracted stay.

Thus, over the period of treatment (for example, applications of effective non-toxic dosage amounts of compositions containing for example effective non-toxic dosage amounts of the NSAIDs and effective non-toxic dosage amounts of the sodium hyaluronate, 3 times a day for 2-4 weeks, transport the NSAIDs to to the epidermis to inhibit prostaglandin synthesis to enable the macrophages to "scavenge" the tumour cells and eliminate them. The end result is the successful treatment of the disease or condition at the site of trauma and/or pathology of the skin or exposed tissue, for example, the resolution of, the basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin, primary and metastatic melanoma in the skin, genital warts cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed

psoriasis), corns on the feet and hair loss on the head of pregnant women, with complete disappearance of the disease or condition as the case may be, by topical therapy without resorting to surgery.

One of the formulations which we have employed successfully is a gel formulation comprising 3% diclofenac in 2.5% sodium hyaluronate formulated as follows:

Formulation 1 (3000 ml.)

Formula	Supplier	(LOT)	Amount	Percent
Glycerine	Life	1043	150 g (119 ml)	5
Benzyl Alcohol	Caledon	02517	90 g (86 ml)	3
Diclofen. : Sodium	Prosintex	9113003	90 grams	3
Sodium Hyaluronate (MW 661,660)	Skymark	HG1003	75 grams	2.5
Sterile water	Baxter	AW4455	2795 ml.	
balance				

Procedure

- set up stirring apparatus using a 4 litre stainless steel beaker
- add water, Glycerine, and Benzyl Alcohol; stir to mix
- add Diclofenac Sodium and stir for 30 minutes
- then add the Sodium Hyaluronate and stir for 90 minutes
- initially, stir at a high torque but avoid splashing; as the gel thickens, stir at a lower torque.

The gel is then packaged in a tube or jar or other suitable container for use. Identification of suitable dosage amounts and how they are taken from the container may be provided with the container - for example squeeze "X" cm. of ribbon from the tube; fill spoon or spatula accompanying jar; (the spoon or spatula containing a predetermined dosage amount) then apply and rub into site of trauma and/or pathology (the dosage amount indicated will be such amount of the composition which comprises in excess of about 5 mg. of sodium hyaluronate per cm² (square centimeter) of skin or exposed tissue to which the dosage amount is to be applied. The amount of Diclofenac Sodium was determined in the same manner (having regard to the dosage amount required).

Another such formulation is:

Formulation 2

Formula	Supplier	(LOT)	Amount	Percent
Methoxypolyethylene Glycol 350	Sigma	34F-0266	300 g.	20
Benzyl Alcohol	BDH	23797	15 g.	1
Diclofenac Sodium	Prosintex	9123012	45 g.	3
10 Sodium Hyaluronate (MW 679,000)	Skymart	HG 1004	37.5 g.	2.5
Sterile Water	Baxter	AW45R6	1200 ml.	
balance				

Procedure

- set up stirring apparatus using a 3 litre stainless steel beaker
- add water, Methoxypolyethylene Glycol 350, and Benzyl Alcohol and stir for 20 minutes to mix
- 20 - add Diclofenac Sodium and stir for 30 minutes to dissolve
- add Hyaluronate Sodium slowly and stir initially at a high speed, but avoid splashing
- after addition, stir at a slower speed for 90 minutes; the slower speed reduces the formation of air bubbles
- 25 the result is a clear, transparent, viscous gel which is put into a container. Once again instructions are given for administration and if applicable measuring devices (to provide a premeasured dosage amount) accompany the container.

30 Still other formulations are:

Formulation 33% Diclofenac in 2.5% HA Gel

	<u>Formula</u>	<u>Supplier</u>	<u>LOT</u>	<u>Amount</u>	<u>Percent</u>
5	Sterile Water	Baxter	AW45K6	1200 ml	-
	Methoxypolyethylene Glycol 350	Sigma	34F-0266	300G (273 ml)	20%
	Benzyl Alcohol	BDH	23797	15G (14 ml)	1%
	Diclofenac Sodium	Prosintex	9123012	45 g	3%
10	Sodium Hyaluronate	Skymart	HG 1004	37.5 g	2.5%
	MW 679,000				

Procedure

15

- Set up stirring apparatus using a 2 liter stainless steel beaker,
- Add water, Methoxypolyethylene Glycol 350, and Benzyl Alcohol and stir for 20 minutes to mix,
- 20 - Add Diclofenac Sodium and stir for 30 minutes to dissolve,
- Add Hyaluronate Sodium slowly and stir initially at a high speed, but avoid splashing,
- After addition, stir at a slower speed for 90 minutes, the slower speed reduces the formation of air bubbles,

25

The result is a clear, transparent, viscous gel which is poured into jars and tubes. Once again instructions accompany the container and where applicable appropriate devices for providing a premeasured amount of the composition accompany the container.

Formulation 4

5% IBUPROFEN IN 3.0% HA GEL, 50 ml JAR

Formula	Supplier	LOT	Amount	Percent
---------	----------	-----	--------	---------

Sterile Water	Baxter	AW45R6	196 ml	--
Meglumine	Falk	15684	11 g	5.5%
Ibuprofen	BDH	19/241	10 g	5%
Benzyl Alcohol	BDH	23797	2 g	1%
Glycerin	BDH	2579	2 g	1%
Hyaluronate Sodium	Skymart	HG 1003	6 g	3%
Mol Wt 661,600				

PROCEDURE

- Set up stirring apparatus using a 300 ml stainless steel beaker,
- Add Sterile Water and Meglumine, and stir for 10 minutes,
- Add Ibuprofen and stir for 15 minutes,
- Add Benzyl Alcohol, followed by Glycerin and stir for 15 minutes,
- Finally, add Hyaluronate Sodium slowly and stir initially at a high torque to mix, but avoid splashing,
- As the gel thickens, stir at a slow speed for 90 minutes.

i) less than about 1% sulphated mucopolysaccharides on a total weight basis;

ii) less than about 0.4% protein on a total weight basis;

5 iii) less than about 100 ppm iron on a total weight basis;

iv) less than about 10 ppm lead on a total weight basis;

v) less than 0.00166% glucosamine;

10 vi) less than 0.0166% glucuronic acid;

vii) less than 0.0166% N-acetylglucosamine;

viii) less than 0.00166% amino acids;

ix) a UV extinction coefficient at 257 nm of less than about 0.23;

15 xi) a UV extinction coefficient at 280 nm of less than 0.19; and

xii) a pH within the range of 7.5-7.7

Applicants also propose to use sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc., having
20 the following specifications:

	<u>Characteristics</u>	<u>Specification</u>
	Appearance	White to cream colored particles
	Odor	No perceptible odor
25	Viscosity Average	< 750,000 Daltons
	Molecular Weight	
	UV/Vis Scan, 190-820nm	Matches reference scan
	OD, 260nm	< 0.25 OD units
	Hyaluronidase Sensitivity	Positive response
30	IR Scan	Matches reference
	pH, 10mg/g solution	6.2 - 7.8
	Water	8% maximum
	Protein	< 0.3 mcg/mg NaHy
	Acetate	< 10.0 mcg/mg NaHy
35	Heavy Metals, maximum ppm	
	As Cd Cr Co Cu Fe Pb Hg Ni	
	2.0 5.0 5.0 10.0 10.0 25.0 10.0 10.0 5.0	
	Microbial Bioburden	None observed
	Endotoxin	< 0.07EU/mg NaHy

Biological Safety Testing

Passes Rabbit Ocular
Toxicity Test

Another form of sodium hyaluronate is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

Specifications' Test

Results

	Lot No.	HG1004
	pH	6.12
10	Chondroitin Sulfate	not detected
	Protein	0.05%
	Heavy Metals	Not more than 20 ppm
	Arsenic	Not more than 2 ppm
	Loss on Drying	2.07%
15	Residue on Ignition	16.69%
	Intrinsic Viscosity	12.75 dl/s (XW: 679,000)
	Nitrogen	3.14%
	Assay	104.1%
	Microbiological Counts	80/g
20	E. coli	Negative
	Mold and Yeast	Not more than 50/g

Other forms of hyaluronic acid and/or its salts, and homologues, derivatives, complexes, esters, fragments and sub units of hyaluronic acid may be chosen from other suppliers, for example those described in prior art documents provided the form of hyaluronic acid chosen is suitable for transport of the medicine.

The following references teach hyaluronic acid, sources thereof, and processes for the manufacture and recovery thereof which may be suitable.

United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

"(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 cm³/g., and preferably greater than about 2000 cm³/g.;

This was an open, repeat dose, crossover comparison using a randomized balanced block in six healthy volunteers.

The study consisted of administration with one, two week period in between periods, each period lasting fourteen days. The test articles applied were for the first six days of each period and the seventh day was study day during which the final application is made and blood samples taken.

The approximate duration of the study including pre and post study screening was six weeks.

10

Doses

Diclofenac (3.0%) with Hyaluronic Acid (2.5%)

Dose: Approximately 2 g, three times daily

Route: Topical

15

(W1) Voltarol Emulgel, Diclofenac diethylammonium salt 1.16g aqueous gel (Geigy)

Dose: Approximately 2 g, three times daily

Route: Topical (W1)

20

ADMINISTRATION: to suitable patients

Subjects applied one of the designated test articles topically to the calves and massaged into the skin, in a dose of approximately 2 g per application three times a day for six consecutive days. The size of a 2g dose was prepared by comparison with a silicone example given to each subject.

On the seventh day, the cream was applied once, in the same manner as before, under the supervision of the staff of the Clinical Investigation Unit.

After a washout period of one week the procedure was repeated with the alternate test article.

The following were the results of the tests:

(H = hyaluronic acid formulation)

(V = Voltarol Emulgel)

PERIOD 1All concentrations ng ml⁻¹

SUBJECT	TIME POINT (hours)											
	0	0.25	0.5	1	2	3	4	5	6	8	10	12
H-1	10.3	7.1	6.4	ND	ND	5.4	6.5	5.1	ND	ND	ND	ND
H-2	ND	5.1	ND	5.1	ND	ND	ND	ND	ND	5.1	ND	ND
ND	ND	ND	5.5	5.2	ND	ND	ND	ND	ND	ND	ND	V-3
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	H-4
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	V-5
ND	ND	ND	ND	ND	ND	ND	8.4	ND	ND	ND	ND	V-6

ND = NONE DETECTED (>5.0 ng ml⁻¹)PERIOD IIAll concentrations ng ml⁻¹

SUBJECT	TIME POINT (hours)											
	0	0.25	0.5	1	2	3	4	5	6	8	10	12
V-1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
V-2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
V-4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

ND = NONE DETECTED (>5.0 ng ml⁻¹)

Other tests were undertaken to determine blood levels comparing Proflex (a formulation containing Ibuprofen) and the following formulation containing hyaluronic acid and Ibuprofen.

HYANALGESE CREAM (L) X PB 022

- 50 ml tube

Quantity 3000 ml

FORMULA

A. Oily Phase		SUPPLIER	LOT	AMOUNT	PERCENT
Liquid Wax DICDD		Brooks/Amisol		450g	15.0%
Brookswax D		Brooks/Amisol		480g	16.0%
Glycerine		Amisol		150g	5.0%
B. Aqueous Phase					
Sterile Water		Baxter	AW4YA8	1950ml	-%
Meglumine		Falk		150g	5.0%
Sodium Hyaluronate		Skymart	PO1	45g	1.5%
MW 207,000					
Ibuprofen		BDH		150g	5.0%
Suttocide A		Sutton		9.0g	0.3%

The following were the results

(A) PROFLEX

5

SUBJECT		Time after administration (Hours)												
Number		PD	0	0.25	0.5	1	2	3	4	5	6	8	10	12
10	1	ND	0.41	0.37	0.37	0.32	0.30	0.27	0.27	0.24	0.37	0.31	0.31	0.16
	2	ND	0.12	0.12	0.08	0.11	0.12	0.12	0.07	0.08	0.09	0.08	ND	0.06
	3	ND	0.09	0.08	0.07	ND	ND	ND	ND	ND	ND	ND	ND	ND
	4	ND	0.12	0.14	0.16	0.11	0.11	0.25	0.24	0.17	0.13	0.16	0.11	0.13
15	5	ND	0.14	0.19	0.19	0.15	0.16	0.16	0.14	0.12	0.11	0.13	0.10	0.07
	6	ND	0.11	0.09	0.09	0.06	0.07	0.05	0.05	0.05	ND	ND	ND	ND
	Mean	0.00	0.17	0.17	0.16	0.13	0.13	0.14	0.13	0.11	0.12	0.11	0.09	0.07
S.D.		0.00		0.12	0.10	0.11	0.10	0.10	0.10	0.10	0.08	0.13	0.11	
		0.12	0.06											

20

(B) HYALURONIC ACID AND IBUPROFEN

SUBJECT		Time after administration (Hours)												
Number		PD	0	0.25	0.5	1	2	3	4	5	6	8	10	12
25	1	ND	0.11	0.11	0.12	0.08	0.08	0.09	0.11	0.12	0.08	0.11	0.16	0.14
	2	ND	0.22	0.21	0.26	0.17	0.24	0.24	0.25	0.23	0.19	0.19	0.20	0.14
	3	ND	0.17	0.10	0.12	0.09	0.08	0.07	0.06	ND	0.06	0.26	0.09	0.05
	4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	5	ND	0.17	0.16	0.16	0.12	0.09	0.10	0.11	0.10	0.09	0.10	0.07	ND
	6	ND	0.07	0.07	0.09	ND	ND	ND	ND	ND	ND	ND	ND	ND
30	Mean	0.00	0.12	0.11	0.13	0.08	0.08	0.08	0.09	0.08	0.07	0.11	0.09	0.06
	S.D.	0.00	0.08	0.07	0.08	0.06	0.08	0.08	0.09	0.09	0.07	0.10	0.08	0.07

ND None detected <0.05 µg/ml

The above clearly indicates that the blood levels are much less using hyaluronic acid to administer the NSAID.

40

PRELIMINARY REPORT

A trial was conducted using a gel composition (Number 109) comprising 3% Diclofenac in 2.5% Hyaluronic Acid as previously described and a composition containing Diclofenac sodium salt 3% but not including any form of hyaluronic acid. (Number 112) The trial was conducted with 60 patients who were randomly assigned to test preparations number 109 or 112. The trial has not been completed as yet but so far 31 patients have finished the protocol. Patients were diagnosed:

50

- 4 Rheumatoid arthritis of the knee
- 8 Myofascial trigger points in the M.trapezius area
- 12 Periarthropathies of knee without effusion
- 7 Periarthropathies with effusion in the knee joint

The 31 patients were aged 22-75 years (27 females, 4 males). All patients were hospitalized. Patients entering the trial were thoroughly examined and type of extraarticular or articular rheumatism assessed.

5

On day 1 baseline pain was assessed on the 10 cm visual analogue scale (VAS) and pain measurement of the quantitative pain sensitivity using a pressure tolerance meter (PTM) were performed. Then test gel - approximately 2.g - was massaged on to the skin of maximum pain. Gels were applied 3 times daily.

10

0.5, 1, 1.5, and 2 hours after morning application measurements of pain sensitivity were carried out and values recorded.

15

This procedure was continued on day 2, 3 and 4; measurements (VAS and PTM) of pain severity were done on day 1, 2 and 4.

20

Prior of the beginning of the study and at the end on day 4, physician's global assessment, assessment of swelling, tenderness and limitation of movement were recorded.

As the study is ongoing statistical evaluation is not yet available. For further details see Table 1.

TABLE 1

25

	Composition	Composition
Reaction	109, n = 16	112, n = 15
Good Alleviation of pain	13	8
30 Moderate Alleviation of pain	2	2
No Alleviation of pain	1	5

35

From the data recorded we have concluded that the patients to whom composition 109 was administered did better in terms of earlier and longer lasting analgesic effect (up to 4 hours) than the 112 composition especially in patients with myofascial trigger points and with periarthropathies of the knee joints without effusions. Neither composition 109 nor

composition 112 treated patients showed any effect on swelling if any swelling exist at all. Systemic side effects have not been observed; one patient to whom composition 112 was administered showed reddening of the skin on the site of application.

Any intake of system NSAIDS, corticosteroids and other analgesics was not allowed one week before and during the trial.

10 EXAMPLES

The following examples are offered to illustrate uses of Applicants' invention.

Example 1

15 A male patient had a number of lesions (basal cell carcinoma), including one on his forehead which was a combination of major "horny epithelium" and some degree of ulceration. After continuous treatment with Formulation 1 (several times per day for several weeks of dosage amounts
20 squeezed from tubes as ribbons of composition), the lesions showed epithelialization, no hemorrhagic areas, and no initiated areas (as they were in the past without our treatment). The "horny epithelium" and ulceration of the forehead lesion were also gone. The patient had a complete
25 successful response with the formulation. All basal cell carcinoma lesions had been resolved and disappeared. There has been no recurrence.

Example 2

30 60 year old male tennis player had sore elbow and basal cell carcinoma on forearm proximate sore elbow. Patient tried Formulation 1 to abate pain in tennis elbow. (Dr. Falk was not treating this patient for anything at the time, did not know of the basal cell proximate the elbow and merely
35 offered the formulation for pain relief of the elbow instucting the patient to squeeze a ribbon of the composition and apply and rub into the sore elbow). However, the formulation "spilled" over onto the Patient's basal cell carcinoma. Patient was planning to have basal cell carcinoma

removed surgically by another doctor, but when the patient returned to see the doctor, the basal cell carcinoma was disappearing (because of spill-over of Formulation 1). Dr. Falk was then advised and treatment was now undertaken by Dr. Falk with direct application of Formulation 1 to the lesion 3 times a day for two additional weeks. After two weeks, the basal cell carcinoma disappeared. There has been no recurrence.

10 Example 3

Male, mid to late 40's had severe basal cell carcinoma on left temple. Doctors recommended its removal by surgery. However, the surgery would have been risky because of the lesion's proximity to facial nerves.

15 Patient saw Dr. Falk who gave him Formulation 2 to be applied in dosage amounts 3 times daily.

After 14 days, 75% of the lesion was gone. Surgery was postponed and the treatment was continued. Application of dosage amounts of Formulation 2 was continued for an additional two weeks. At the end of the 2-week period, the lesion was completely resolved and disappeared without any surgery being required. There has been no recurrence.

Example 4

25 Male, early 40's, had recurrent actinic keratoses lesion on his right temple. Early attempts at removal by third parties involved the application of liquid nitrogen (twice) without final resolution. The lesion kept recurring. The patient was sent to Dr. Falk who treated the lesion with Formulation 1 with applications of dosage amounts 3 times daily for 7 days. After 7 days, the lesion was completely resolved with no subsequent recurrence.

Example 5

35 A male patient suffering from kyphosis suffered from constant back pain. Taking analgesics orally and rubbing back preparations onto his back did little to alleviate the back pain. When NSAIDs in hyaluronic acid (sodium hyaluronate)

her pain decreased dramatically and her skin and bone involvements steadily improved.

TOPICAL DICLOFENAC ACID 3% IN HYALURONIC ACID GEL (2.5%) BASE

A practitioner reviewed the effectiveness of topical Diclofenac Acid 3% in hyaluronic acid gel (2.5%) base in acute traumatic injuries of no longer than 3 days duration. The cases were all in the spectrum of ages between 18 and 65. Normal exclusion criteria were followed regarding exclusion of pregnancy, aspirin or N.S.A.I.D., allergies or active peptic ulceration.

As an overall, the following impressions were gained from 30 cases:

1. The topical H.D. (composition comprising sodium hyaluronate and diclofenac) had an obvious analgesic action with onset occurring rapidly within one hour; this is a phenomenon not obviously seen with other non-steroidals that we have used.
2. There was a very definite patient acceptance of the gel as a form of treatment, being logical, easy to apply, without local or systemic side effects, rapid absorption with no staining of clothing.
3. The anti-inflammatory action was equivalent on a "questimate" based on experience of similar injuries to oral N.S.A.I.D.s, without the threat or risk of side effects.

In summary, compared with other topical N.S.A.I.D.s the analgesic effect is distinct, the anti-inflammatory is equal to oral N.S.A.I.D.s and the patients' acceptance is far superior to any other diclofenac or piroxicam topical that the practitioner evaluated.

Following the practitioner's basic preamble regarding the parallelism of topical N.S.A.I.D.s and topical steroids, the practitioner has used the former in contact dermatitis, insect bites and T.V. eczema, all with very positive effects, again pointing direction to trials of a double blind nature in these fields.

were applied directly to the back, the back pain eased and disappeared.

With indomethacin (dissolved in N-methyl glucamine) and naproxen both dissolved in hyaluronic acid, the patient experienced some side effects. However, with Toradol™ (the [+/-] form tromethamine salt of ketorolac - a prostaglandin biosynthesis inhibitor and analgesic and anti-inflammatory, the back pain eased and disappeared for some time and there were no side effects. The compositions were applied generously onto the sites of back pain.

Example 6

A male patient with basal cell carcinoma was first treated by an oncologist who attempted to surgically excise the lesion (without success) and then irradiated the lesion again without success. The patient then attended before Dr. Falk who applied Applicant's formulation (diclofenac with sodium hyaluronate and excipients). Application was made three times daily for about a month and the lesion disappeared. Some excoriation anterior and slightly superior developed over the last two weeks but was cleared by the application of hyaluronic acid by itself.

This resolution clearly indicates that even with prior applications of unsuccessful therapies (surgery and irradiation), Applicant's formulations can be used successfully.

Example 7

In another patient, a drug (methotrexate) was carried in hyaluronic acid and applied topically to a patient with psoriasis. The formulation was absorbed and the psoriasis cleared.

Example 8

A patient with dermal (skin) metastases in a fibratic scar form and metastatic cancer in the form of musculoskeletal involvement in her thorax.

On topical application of our formulation comprising diclofenac (Voltaren) in hyaluronic acid (sodium hyaluronate),

CHRONIC CONDITIONS - EVALUATIONS

2.5% HYALURONIC ACID WITH 3% DICLOFENIC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	LA (M)	11.04.56		Hyper- aesthesia	Severe discomfort following extensive surgery to dorsal spine with insertion of rods in 1989. Even contact with clothes produced sig- nificant discomfort. Initially treated with EMLA with only transient anaes- thetic results, however even after 3 days treatment with Hyal diclofenac acid noticed marked decrease in supersensitivity which has continued for at least 4 weeks while still using gel.	P Example of peripheral action on super- sensitiza- tion of nerve ending queried.
15						
20						
25	KB (F)	08.06.58		Chronic chondro- malacia perhaps dating back to 1976.	Treated right knee which was worse initially and was amazed at the response, then started to treat left knee that was not so painful, again with positive response Here we have a built-in con- trol.	P
30						
35	DB (F)			Chronic neurogenic pain in ankle with associated dysaesthesia	Initially felt some improve- ment which was not continued although initially quite positive - query placebo reaction.	N
40	DC (F)	07.11.51		Chronic back pain - query due to facet syndrome or trigger points, really diag- nosis uncertain.		N
45						
50						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	CC	18.01.25		Chronic capsulitis right hip right knee	Definite effect over knee where application to target distance short. No obvious effect over hip.	P
15	AG (F)	07.11.58		Myositis in rhomboids muscles following motor vehicle accident	Initially given placebo in error, only marginal or minimal effect, if any. Found active to be effective while being used, did not cure condition which needed trigger point therapy.	P
20						
25	CH (F)	22.08.61		Chronic relapsing tendonitis right elbow	No significant effect, nor has aggressive therapy since including injection with cortisone and numerous opinions.	N
30	SH (F)	16.07.55		Tendonitis and myositis	Control of tendonitis while using preparation. Is now back at work.	P
35	DM (M)	17.06.47		Neuritis	This patient has a very unusual pain in his left groin following nerve injury, with the use of preparation noticed decrease in pain sensation while on medication. Hyperaesthesia altered although pain (which may be phantom) still present.	U
40						
45	PJ	15.06.45		Capsulitis of right wrist	Symptoms improved 50% while using Hyal diclofenac acid, however, on discontinuation pain reappeared. Exact etiology uncertain.	U
50						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	DJ (F)			Dorsal myositis	Control while using gel equal and with less side effects than tiger balm. Controlled symptoms while using medication. Exact diagnosis as to cause of myositis uncertain.	P
15						
20	DK (F)	27.08.38		Severe capsulitis left shoulder	This patient has had capsu- litis left shoulder for many years and treated with only transient relief with corti- sone injections. poor relief with topical piroxicam. Was started on topical diclo- fenac acid and noticed relief of pain in 20 minutes continuing for 4 - 6 hours. See letter March 11/92. At present is using H.D. regu- larly, has found it to be useful in other areas of chronic pain. Is President North American Chronic Pain Association, has good insight into medication and placebos etc. Has two D.C.S. implants.	P Extremely rewarding case
25						
30						
35						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	JL (M)	10.12.45		Chronic myositis secondary to query facet syndrome	Pain has failed to respond to many aggressive treat- ments.	N
15	RMC (F)	13.06.57		Neuronitis following facet rhizotomy with result- ing pain in her back	It is a difficult case with considerable overlay, she obtained some relief with H.D., would estimate 30-40% Interestingly hyper- anaesthesia was decreased.	U
20						
25	RM (F)	20.08.52 P		Chronic capsulitis	Using H.D. significant improvement in pain while used, on stopping treatment recurrence of pain, needed intra-articular cortisone.	
30	GM (F)			Sub-acute tendonitis right ankle	Rapid resolution of pain within one day and positive return of function.	P
35	PM (F)	20.09.46		Acute on chronic osteo- arthritis of first meta- tarsal phalyngeal joints	Rapid analgesic response with rapid settlement.	P
40						
45	DN (F)	10.03.44 P		Chronic fasciitis of feet	Excellent response to appli- cation of H.D. with occlu- sion. Had failed to respond to oral N.S.A.I.D.s and physiotherapy. Query posi- tive result due to short application target distance in a vascular tissue.	
50						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENIC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	BP (F)	04.03.20		Severe chronic arthritis of the knee. Unable to take oral	Initially one knee treated with such good results that both knees treated, see letter. Not only did pain decrease but marked swell- ing around knees. Signifi-	P Side effects- non/Inci- dental
15				N.S.A.I.D.s	cant relief of pain and increase in movement as a result of this and perhaps reduction of swelling.	resolution of area of thrombo- phlebitis below area
20					<u>Intrestingly has severe superficial varicose veins developed thrombophlebitis around right knee and the area treated by chance showed far less redness and tenderness than the throm- bophlebitis below this area.</u>	of treat ment
25						
30	SP (M)	06.11.48		Idio- pathic diffuse capsulitis of hands	Has had similar episodes with poor response to many treatments including N.S.A.I.D.s per os	U
35	WS	04.06.45		Chronic neurionitis due to injury to lateral cutaneous nerve of thigh	Has been exposed to number- ous treatments including tow attempts of surgery without effect. There is decrease in hyperaesthesia but no change in pain.	U
40						
45	MS (F)	04.06.28		Chronic capsulitis	Failed to respond to number of treatments, good back- ground resolution of pain, however, still had acute pain with certain movements.	P
50						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	IS (F)	15.01.48		Chronic capsulitis	Had failed to respond to numerous treatments including oral and topical N.S.A.I.D.s Using H.D. there was equivalent control of pain as with other therapies which lasted while medication was used. Referred for surgical opinion.	P
15						
20	GS (F)	26.03.47		Chronic tendo- sinovitis	Oral diclofenac acid dis- continued due to gastritis and also history of ulcer- ation. Control using H.D. equal to or better than oral N.S.A.I.D.s.	P
25						
30	VK (F)	01.01.39		Chronic tendonitis	Good relief of pain and tenderness while using H.D. however on discontinuation of gel symptoms returned, treated with intramuscular steroids.	P for pain N for resolution
35	GH (M)	03.11.21		Acute on chronic osteo- arthritis left hand	In view of age and general parous medical condition, ideal for topical. Had been previously on topical piroxicam for left shoulder capsulitis.	P Commented on better absorption compared to topical piroxicam
40						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	JA (M)	06.02.58		Severe post-traumatic and surgical osteoarthritis of left leg with staples. Poor result to oral N.S.A.I.D.s also gastric irritation.	Produced good superficial analgesia especially where staples were irritating subcutaneous tissue, little effect on deeper, severe osteoarthritic pain of knee. This pain was of considerable severity, needing narcotics.	P
15						
20	IM (M)	30.11.51		Chronic superficial myositis	Severe rhomboid inflammation right side, treated with H.D., very definite improvement in pain and tenderness.	P
25	TK (F)	23.04.70		Acute on chronic capsulitis due to sports injury right hand	Excellent rapid analgesic followed by anti-inflammatory response in young women who could not take oral N.S.A.I.D.s due to past gastritis.	P
30						
35	AD (F)	03.01.49		Chronic diffuse pain thought to be myositis	Poor response to H.D. After intensive investigation and numerous consultations and treatment, pain still undiagnosed and unresponsive.	N
40	NH (F)	25.03.25		Subacute capsulitis right ankle	Excellent response analgesic and anti-inflammatory-wise within a few days. Marked clinical improvement. In view of this patient's parous general medical condition and hypertension, not suitable for oral NSAIDs.	P
45						
50						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5	MD	18.04.34		Subacute rheumatoid arthritis	Had failed to respond to oral N.S.A.I.D.s, which caused gastritis, tried on topical piroxicam with nega- tive effects. Negative response to H.D.	N
10						
15	MW (F)	07.05.46		Heberden's nodes, pain- ful, swollen causing difficulty in movement	Very slow positive outcome, initially improvement in pain followed by reduction in swelling. Etiology of this condition is unknown, partly genetic. Would have been interesting to treat alternate digits, plus or minus thermographic confir- mation.	P
20						
25	LP (F)	20.07.23		Acute on sub-acute osteo- arthritis of the hands with Heberden's nodes	Initially treated with Idarac, poor response over- all, some improvement in generalised arthritis of hands but none on Heberden's nodes. Pain flared on stop- ping Idarac due to gastritis. Started on H.D., especially favourable results with sub- sidence of tenderness of nodes and settling of arthritis. Interestingly enough, no flare up on dis- continuation after one month.	P
30						
35						
40						

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

	Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
5						
10	JG (F)	24.11.50		Post facet rhizotomy hyper- aesthesia, with marked pain and hyper- aesthesia between scapulae	Had failed to respond to oral N.S.A.I.D.s and E.M.L.A. Application of H.D. improved the surface pain significantly but had no effect on the deeper pain. My impression was that the deeper pain was due to section of the facet nerve and beyond the reach of the topical medication. There is little doubt that the skin sensitivity was decreased.	U
15						
20						
25	SW (F)	10.09.39		Knee pain due to chondro malacia	Upset in past due to oral N.S.A.I.D.s., also hyper- tension made one loathe to use this medication with serum levels. Good anal- gesic and anti-inflammatory action, however on discon- tinuation pain flared. Seen for arthroscopic surgery with relief of pain.	P (Effec- tive while being used) Condition only cured by surgery
30						
35						

* Two types of pain-response in only one

1. Interestingly in the whole series, there was not one case of local side effects and as expected from past studies, no general or systemic. Since this report was prepared we have had one case of mild folliculitis which responded to discontinuation of treatment, will rechallenge.

2. A number of patients commented that they felt the gel improved the texture and softness of their skin, and commented that it was messy or stained their clothes.

3. In one case of topical thrombophlebitis where the inflamed vein crossed the area of treatment, the vein in the area of treatment improved while that outside at a distance did not. Again, similar to using oral N.S.A.I.D.s. ***.

Photographs were taken of patients with basal cell carcinoma Figures 1-6 photographs, and of mice with tumors induced in the skin of the hind legs (Figure 7 photographs). The patients were treated by using combinations of NSAIDS, (non-steroidal anti-inflammatory drugs) and hyaluronic acid (including sodium hyaluronate) according to the invention (3% diclofenac in 2.5% sodium hyaluronate gel base). Each of the six sets of Figures made up of photographs of the different persons should include a legend describing or explaining each picture as follows:

Legend for Figures 1A and 1B should read:

Patient : W.D., male, 82 years
 Diagnosis: Basal cell carcinoma
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 1A: June, 1991
 Figure 1B: December, 1991

Legend for Figures 2A and 2B should read:

Patient : M.F., male, 45 years
 Diagnosis: Basal cell carcinoma
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 2A: January, 1992
 Figure 2B: April, 1992

Legend for Figures 3A, 3B, 3C and 3D should read:

Patient : H.A., male, 82 years
 Diagnosis: Basal cell carcinoma
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 3A: January 26, 1992
 Figure 3B: March 16, 1992
 Figure 3C: January 26, 1992
 Figure 3D: March 16, 1992

Legend for Figures 4A, 4B, 4C and 4D should read:

Patient : R.F., male, 64 years
 Diagnosis: Basal cell carcinoma
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 4A: January 26, 1992
 Figure 4B: March 16, 1992
 Figure 4C: January 26, 1992
 Figure 4D: March 16, 1992

Legend for Figures 5A, 5B, 5C and 5D should read:

Patient : R.W., male, 86 years
 Diagnosis: Basal cell carcinoma ;
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 5A: January 26, 1992
 Figure 5B: March 16, 1992
 Figure 5C: January 26, 1992 untreated
 Figure 5D: March 16, 1992 untreated

Legend for Figures 6A, 6B and 6C should read:

Patient : E.D., female, 70 years
 Diagnosis: Basal cell carcinoma
 Treatment: NSAIDS plus HA gel. 3 times per day
 Figure 6A: April 20, 1992
 Figure 6B: May 13, 1992
 Figure 6C: July 7, 1992

The Legend for Figure 7 (Figures 7A and 7B) relate to:

Mouse Strain: DBA₂
 Tumour: p815
 Figure 7A: control, 19 days
 Figure 7B: Novantrone plus HA gel 19 days

The mice shown in Figures 7A and 7B had tumours induced in the skin of their hind legs and dosage amounts (2ml) of Novatrone (10 mg. per dosage amount) (MITOXANTRONE (t.m.) and 2.5% sodium hyaluronate were applied (rubbed onto) the skin at the site of the pathology. The tumours reduced in size (See Figure 7B) clearly illustrating the percutaneous delivery of the medicine by the hyaluronic acid. (See Figure 7).

The following additional comments are made with respect to the patients.

With respect to R.W. and Figure 5, the reader will note in Figures 5a and 5c the patient suffered from basal cell carcinoma on his back (Figure 5c) and his temple (Figure 5a). Because of the age of the individual (86) the basal cell carcinoma on his back could not be reached by him for application of the medication. Thus the basal cell carcinoma in 5c remained untreated and grew (see Figure 5d). However, the portion indicated in 5a on his temple could be reached and after application of the basal cell carcinoma formulation to

The effect of Hyaluronic acid as a drug carrier of anti-cancer agent (5-FU) 5-Fluoracil was also studied.

(Intratumour injection study)

5 B. EXPERIMENTAL MODEL (2)

1. Method and Material

a. Animal : Fisher 344 rat, male

200-250g

b. Tumor model

Fisher Bladder Carcinoma

Tumor (2mm viable tumor fragment) was transplanted subcutaneously on the right flank by trocar

c. Treatment was started when tumor size is about 1.5 cm.

(2 weeks after implantation.)

1. These drugs were administrated by intratumor injection.

(right flank)

At the same time, injection into normal skin (left flank) was carried out similarly.

Group A : H-5-FU 5mg/kg + saline /0.3ml (i.t.)

B : H-5-FU 5mg/kg + HA 15 mg/kg /0.3ml (s.c.)

3H-FU without or with HA was injected as a single dose (0.3ml) into the center of the tumor (on the right flank) with a 30 gauge needle. At the same time, injection into normal skin (on the left flank) was carried out similarly.

The tumor and skin was then removed at different times (1h, 6hr) for counting radioactivity of the remaining content in the tissue.

2. Result

All the results were expressed as Mean - S.E. under the following headings:

3	TUMOR TISSUE (left hand portion of the graph)	NORMAL SKIN (Right hand portion of the graph)
10	<div> <div></div> 5-FU+HA group(n=4) <div></div> 5-FU group(n=4) </div>	<div> <div></div> 5-FU+HA group(n=4) <div></div> 5-FU group(n=4) </div>

(See Figure 4 of Page 4/12)

3. Conclusion

1. In 5-FU HA group radioactivity was accumulated and retained in the tumor tissue for a long period, whereas rapid clearance was demonstrated in normal tissue. (skin)

2. In 5-FU group, radioactivity immediately disappeared from the tumor or the normal tissue by diffusion, primarily into blood capillaries.
 ---- SFU can traverse freely between the interstitial space and blood capillary.

23 The Effect of Hyaluronic Acid as a Drug Carrier in Target Cancer Chemotherapy

A. EXPERIMENTAL MODEL (1) Intravenous Injection

1. Method and Material

a. Animal : Fisher 344 rat, male
200-250g

b. Tumor model

Fisher Bladder Carcinoma

Tumor (2mm viable tumor fragment) was transplanted subcutaneously on the right flank by trocar

c. Treatment was started when tumor size is about 1.5 cm. (2 weeks after implantation.)....tumor weight: $1.0 \pm 0.3g$

The drug was administered Intravenously (through the penile vein)

Group A : 5-FU 20mg/kg (3H-5-FU30 μ Ci) + saline

B : 5-FU 20mg/kg (3H-5-FU30 μ Ci) + HA 15mg/kg

C : 5-FU 20mg/kg (3H-5-FU30 μ Ci) + HA 15mg/kg
+ (3H-HA30 μ Ci)

2. Sample Collection

a. accumulation of ADR, 5-FU in tumor tissue and liver

(1). Tumor was surgically removed (and blood was collected) at *predetermined time after drug administration. Tumor weight was measured (and blood was centrifuged to obtain a plasma sample.)

* 15min, 60 min, 3hr, 4hrs,..... after drug administration.....

Liver was removed for radioactivity counting at the same time.

(2). Radioactivity level in tumor tissue was counted, using a liquid scintillation counter.

3. Conclusion

Radioactivity in Tumor Tissue and Liver

			Tumor	Liver
5	15min	3H-5FU (n=6)	2810±165	18680±625
		3H-5FU+HA (n=6)	352±190	23593±1460
		3H-5FU+3H-HA (n=4)	4087±681	32060±2145
10	60min	3H-5FU (n=3)	1751±149	5451±841
		3H-5FU+HA (n=4)	2599±489	8265±1849
15	3hrs	3H-5FU (n=6)	1493±227	2230±449
		3H-5FU+HA (n=6)	2512±449	2897±340
		3H-5FU+3H-HA (n=4)	3606±929	6977±1633
20	5hrs	3H-FU (n=3)	853±129	1129±70
		3H-5FU+HA (n=3)	1981±479	1754±248
		3H-5FU+3H-HA (n=3)	2168±163	3018±325

mean± S.E.

HA : 15 mg/kg (30μCi/kg)

5-FU : 20mg/kg (30μCi/kg)

See Figure 5' of Page 5/12 of the Figures which comprises a graph entitled "RADIOACTIVITY IN TUMOR TISSUE" comparing CPM on the vertical with time in Minutes on the horizontal (for example 100, 200, 300).

1. Radioactivity in tumor tissue in 5-FU + HA group is higher than that in 5-FU group. There is significant difference

(p>0.05, ANOVA) between with and without HA at 3hrs after injection. The high intratumor concentration was retained for a prolonged time in 5-FU+HA group. (This retention was confirmed by the intratumor injection study.)

2. These results teach that HA can enhance 5-FU uptake in tumor tissue. This phenomenon results from HA distribution (in tumor tissue HA may be lost from the extracellular matrix) and the vascular uniqueness of tumor tissue (hyperpermiability of tumor vessels to macromolecular drug, HA).

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

The claims defining the invention are as follows:

1. A pharmaceutical composition comprising a plurality of effective non-toxic dosage amounts of a composition, each such dosage amount comprising a therapeutically effective non-toxic dosage amount of a drug for the treatment of a disease or condition of the skin or exposed tissue at the site of the pathology or trauma and an effective non-toxic dosage amount of at least 5mg/cm² of a form of hyaluronic acid selected from hyaluronic acid and salts thereof to transport the drug to the site of the pathology or trauma of the disease or condition, wherein the molecular weight of the form of hyaluronic acid is less than 750,000 Daltons and greater than 150,000 Daltons.

2. The pharmaceutical composition of claim 1, wherein each of the plurality of effective non-toxic dosage amounts of the composition making up the pharmaceutical composition comprises at least about 10mg of the form of hyaluronic acid per cm² of the skin or exposed tissue to which the composition is to be applied.

3. The pharmaceutical composition of claim 1 or 2 wherein the form of hyaluronic acid is sodium hyaluronate.

4. The pharmaceutical composition of any one of claims 1 to 3 wherein the disease or condition of the skin or exposed tissue at the site of the trauma or pathology is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies or tumours in the skin, genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis, corns on the feet and hair loss on the head of pregnant women.

5. The pharmaceutical composition of any one of claims 1 to 4 wherein the drug comprises an effective non-toxic dosage amount which inhibits prostaglandin synthesis.

6. The pharmaceutical composition of claim 5 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

7. The pharmaceutical composition of any one of claims 1 to 4 wherein the drug is an anti-cancer drug.

8. The pharmaceutical composition of claim 7 wherein the anti-cancer drug is selected from novantrone.

9. The pharmaceutical composition of claim 6 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

10. The pharmaceutical composition of claim 6 wherein the NSAID is selected from ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

11. A topically applicable percutaneous penetrating and best targeting the epidermis systemic independent acting pharmaceutical composition comprising a plurality of dosage

amounts, each dosage amount comprising, a therapeutically effective non-toxic dosage amount to treat and to assist to resolve a disease or condition of the skin and exposed tissue, selected from at least one of the group consisting of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, malignancies or tumours of the skin primary and metastatic melanoma in the skin, genital warts, condyloma acuminata, cervical cancer, and Human Papilloma Virus including HPV of the cervix, psoriasis, both plaque-type psoriasis and nail bed psoriasis, corns on the feet and hair loss on the head of pregnant women, non-toxic to the patient dosage amount of a non-steroidal anti-inflammatory drug (NSAID) selected from the group consisting of diclonfenac, diclofenac sodium, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac and an effective non-toxic amount of at least 5 gm/cm² of the skin or tissue to which the effective dosage amount is to be applied, of a form of hyaluronic acid selected from hyaluronic acid and pharmaceutically acceptable salts thereof to facilitate the non-steroidal anti-inflammatory drug's rapid transport by the form of the hyaluronic acid to the site in the skin including the epidermis or exposed tissue of the disease or condition into the tissue to remain there for a prolonged period of time to assist to treat and assist to resolve the disease or condition by blocking prostaglandin synthesis wherein the percentage of the composition of the form of hyaluronic acid is about 1-1/2% by weight of the composition and has a molecular weight of between 150,000 Daltons and less than 750,000 Daltons and the non-steroidal anti-inflammatory agent is about 3% by weight of the composition.

12. The pharmaceutical composition of claim 11 wherein the effective non-toxic dosage amount of the form of hyaluronic acid to transport the drug into the skin or exposed tissue exceeds about 10mg for each 1cm² of the skin or exposed tissue area of the disease or condition to which the dosage amount is to be applied.

13. The pharmaceutical composition of claim 12 wherein the molecular weight of the form of hyaluronic acid is less than about 225,000 Daltons.

14. A pharmaceutical composition comprising:

(1) a medical or therapeutic agent in a therapeutically effective amount to treat disease or condition of the skin or exposed tissue; and

(2) a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof,

characterised in that said composition is in such an amount and in such form that (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site of the skin or exposed tissue to be treated, and (ii) component (2) is immediately available to transport (facilitate or cause the transport of) component (1) to the

site of trauma or pathology of the disease or condition to be treated, percutaneously into the skin or exposed tissue where the composition resides and accumulates for a prolonged period, and which component (2) is in an effective non-toxic dosage amount of at least 5mg/cm² of the skin or exposed tissue to transport component (1) upon administration, percutaneously into the skin or exposed tissue to the site of the trauma or pathology.

15 15. The composition of claim 14 wherein the form of hyaluronic acid is sodium hyaluronate.

16. The composition of claim 14 or 15 wherein the effective amount of the form of hyaluronic acid in the composition exceeds 10mg per square centimetre (cm²) of skin or exposed tissue to which it is to be applied.

17. The composition of any one of claims 14 to 16 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 Daltons.

18. The composition of any one of claims 14 to 17 wherein the drug is a non-steroidal anti-inflammatory (NSAID).

15 19. The composition of any one of claims 14 to 17 wherein the drug is an anti-cancer agent.

20. The pharmaceutical composition of any one of claims 14 to 19 including pharmaceutically compatible excipients to provide a form for ease of administration to the skin or exposed tissue for transport into the epidermis.

20 21. The pharmaceutical composition of claim 20 comprising a gel squeezed from a tube as a ribbon of gel and which dosage amount is in the form of the ribbon of gel "X" cm long containing the effective non-toxic amounts of the drug and form of hyaluronic acids.

22. The pharmaceutical composition of claim 20 comprising a cream taken from a jar to be scooped from a jar in a dosage amount comprising the effective amount of drug and effective amount of the form of hyaluronic acid.

23. The pharmaceutical composition of claim 20 comprising a form selected from a gel, lotion or cream.

24. A composition from which effective dosage amounts may be taken and applied to human skin or exposed tissue suffering pain, the composition comprising a plurality of dosage amounts which may be taken and applied, each dosage amount comprising an effective non-toxic dosage amount of a non-steroidal anti-inflammatory drug (NSAID) and an effective non-toxic dosage amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof hyaluronic acid exceeding 10 mg. per square cm (cm²) of skin or exposed tissue to which it is applied, for percutaneous transport of the NSAID by the form of hyaluronic acid into the epidermis proximate the paccinian nerve bundles to abate the pain.

25. The composition of claim 24 wherein the form of hyaluronic acid is sodium hyaluronate.

26. The composition of claim 24 or 25 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 Daltons and greater than 150,000 Daltons.

27. The composition of any one of claims 24 to 26 in a container including means for assisting the discharge of an effective dosage amount from the container.

28. The composition of claim 27 wherein the container is a tube and said means comprises a mouth opening of predetermined diameter through which the effective dosage amount of the composition is discharged.

29. A dosage amount of pharmaceutical composition comprising: 5% by weight glycerine, 3% by weight benzyl alcohol, 3% by weight diclofenac sodium, 2.5% by weight sodium hyaluronate having a molecular weight greater than 150,000 daltons and less than 750,000 daltons, and sterile water in a container.

30. A dosage amount of pharmaceutical composition suitable for topical application comprising 20% by weight methoxypolyethylene glycol, 1% by weight benzyl alcohol, 3% by weight diclofenac sodium, 2.5% by weight sodium hyaluronate having a molecular weight greater than 150,000 daltons and less than 750,000 daltons, and sterile water in a container.

31. The composition of claim 29 or 30 wherein the sodium hyaluronate has a molecular weight less than 750,000 Daltons and greater than 150,000 Daltons.

32. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 3% by weight of the composition of glycerine, 1.5% by weight of the composition of benzyl alcohol, 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 Daltons, 3% by weight of the composition of liquid wax and sterile water, characterised in that the said pharmaceutical composition is 1500gm, said composition is in a dosage form and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation in the epidermis before passage therefrom.

33. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 5% by weight of the composition of glycerine, 3% by weight of the composition of benzyl alcohol, 3% by weight

of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 Daltons and sterile water, characterised in that the said pharmaceutical composition is 3000gm, said composition is in a dosage form and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

34. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 20% by weight of the composition of methoxypolyethylene glycol, 1% by weight of the composition of benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 Daltons and sterile water, characterised in that the said pharmaceutical composition is 1600gm, said composition is in a dosage form and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

35. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 20% by weight of the composition of a solubiliser, methoxypolyethylene glycol, 1% by weight of the composition of a preservative, benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having molecular weight of 679,000 Daltons and sterile water, characterised in that the said pharmaceutical composition is 1600gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

36. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 5.5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen, 1% by weight of the composition of benzyl alcohol, 1% by weight of the composition of glycerin, 3% by weight of the composition of sodium hyaluronate, having a molecular weight of 661,660 Daltons and sterile water, characterised in that the said pharmaceutical composition is 227gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

37. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amount can be taken comprising: 4% by weight of the composition of meglumine, 2% by weight of the composition of piroxicam, 2.5% by weight of the composition of sodium hyaluronate, having a molecular weight of 661,600 Daltons and sterile water, characterised in that the said pharmaceutical composition is 217gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

38. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: an oily phase comprising 15% by weight of the composition of a liquid wax, 16% by weight of the composition of a wax and 5% by weight of the composition of glycerin; and an aqueous phase comprising 5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen, 1.5% by weight of the composition of sodium hyaluronate having a molecular weight of 200,000 Daltons and 0.3% by weight of the composition of a preservative, suttocide A and sterile water, characterised in that the said pharmaceutical composition is 3384gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to

be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

5 39. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 3% by weight of the composition of glycerin, 1.5% by weight of the composition of benzyl alcohol, 3% by weight of the composition of liquid wax, 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000
10 Daltons and sterile water, characterized in that the said pharmaceutical composition is 3100 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the
15 epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

40. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 1.5% by weight of
20 the composition of a preservative, benzyl alcohol, 3% by weight of the composition of glycerin, about 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of liquid wax, 3% by weight of the composition of sodium hyaluronate having a molecular weight is 661,600 Daltons, and sterile water characterized in that the said pharmaceutical composition is about 1550 gm, said composition is in a dosage form and
25 comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on
30 application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

41. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: an oily phase comprising 15% by weight of the composition of a liquid wax, 16% by weight of the
35 composition of a wax and 5% by weight of the composition of glycerine; and an aqueous phase comprising 5% by weight of the composition of meglumine, 1.5% by weight of the

composition of sodium hyaluronate having a molecular weight 207,000 Daltons, 5% by weight of the composition of ibuprofen and a 0.3% by weight of the composition of a preservative, sutocide and sterile water, characterized in that the said pharmaceutical composition is 3385 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposed tissue for accumulation therein in the epidermis before passage therefrom.

42. A multidose multigram pharmaceutical composition from which a substantial number of effective non-toxic dosage amounts can be taken comprising: 2.5% by weight of the composition of sodium hyaluronate having a molecular weight is 661,600 Daltons, 1% by weight of the composition of flunixin meglumine and sterile water, characterized in that the said pharmaceutical composition s 3000 gm, said composition is in a dosage form and comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition in the skin or exposed tissue on application to the skin or exposes tissue for accumulation therein in the epidermis before passage therefrom.

43. A method of treating a disease or condition of the skin or exposed tissue comprising administering topically a non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable fro topical application, a therapeutically effective non-toxic dosage amount of a drug which inhibits prostaglandin synthesis, and an effective non-toxic dosage amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof to transport the drug into the skin or exposed tissue at the site of the disease or condition to be treated percutaneously into epidermis by ribbing the composition into the skin or exposed tissue and wherein the concentration of the drug is 1-5% by weight and the concentration of the form or hyaluronic acid is 1-3% by weight of the composition.

44. The method of claim 43 wherein the form of hyaluronic acid is sodium hyaluronate.

45. The method of claim 43 or 44 wherein the amount of the hyaluronic acid exceeds about 5mg/cm² of the skin or exposed tissue to which the dosage amount of the composition is applied.

46. The method of any one of claims 43 to 45 wherein the molecular weight of the form of hyaluronic acid is less than about 225, 000 Daltons and greater than 150,000 daltons.

47. The method of any one of claims 43 to 46 wherein the treatment is applied daily for a number of weeks.

48. The method of any one of claims 43 to 47 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

49. The method of claim 48 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

50. The method of claim 48 wherein the NSAID is selected from ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

51. The method of treatment of any one of claims 48 to 50 wherein the treatment comprises applying effective dosage amounts of the composition, a number of times daily for a period of weeks to clear the trauma or pathology.

52. A method or percutaneous delivery of a therapeutically effective dosage amount of a drug which inhibits prostaglandin synthesis in a pharmaceutical composition the drug being transported to the site of trauma or pathology of the skin or exposed tissue of a human to treat a disease or condition or the skin or exposed tissue the delivery comprising topically administering to the skin or exposed tissue, the therapeutically effective non-toxic dosage amount of the drug which inhibits prostaglandin synthesis, in a composition which comprises an effective non-toxic amount of hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons sufficient to transport the drug to the epidermis of the skin to the site of the trauma or pathology to block the synthesis of prostaglandins and wherein the concentration of the drug is 1-5% by weight and the concentration of the form of hyaluronic acid is 1-3% by weight of the composition.

53. The method of claim 52 wherein the amount of hyaluronic acid or salts thereof exceeds at least about 5 mg/cm² of the skin or exposed tissue to which the composition is to be applied.

54. The method of claim 52 or 53 wherein the molecular weight of the hyaluronic acid or salts thereof is less than about 750,000 Daltons.

55. The method of any one of claims 52 to 54 wherein the drug comprises an anti-cancer drug for administration to a tumour or malignancy in the skin or exposed tissue.

56. The method of claim 55 wherein the drug is 10 mg of novantrone in the dosage amount of the composition and the hyaluronic acid or salts thereof is in excess of about 5 mg

of sodium hyaluronic per cm^2 of the skin or exposed tissue for the percutaneous transport of the novantrone.

57. A method of abating pain in skin or exposed tissue of a human suffering from a disease or condition comprising administering a composition comprising an effective non-toxic dosage amount of a drug which relieves pain and an effective non-toxic dosage amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons selected from hyaluronic acid and salts thereof in an amount exceeding 10 per square cm (cm^2) of the skin or exposed tissue to which it is applied for percutaneous transport of the drug by the form of hyaluronic acid into the epidermis proximate the paccinian nerve bundles to give pain relief.

58. The method of abating pain of claim 57 wherein the form of hyaluronic acid is sodium hyaluronate.

59. The method of claim 57 or 58 wherein the drug is a non-steroid anti-inflammatory drug (NSAID).

60. The method of any one of claims 57 to 59 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 Daltons and greater than 150,000 Daltons.

61. A method of treating a disease or condition selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus (HPV), Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated.

62. A method of treating pain topically, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat pain or the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

5 characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of
10 trauma or pathology of pain to be treated, in the skin or exposed tissue.

63. The method of claim 61 wherein component (2) is sodium hyaluronate.

64. The method of claim 62 wherein component (2) is sodium hyaluronate.

65. The method of any one of claims 61 to 64 wherein component (1) is a non-steroidal anti-inflammatory drug (NSAID).

15 66. The method of claim 63 or 64 wherein component (2) is sodium hyaluronate whose molecular weight is between 150,000 Daltons and 225,000 Daltons.

67. The method of claim 65 wherein the NSAID is selected from diclofenac, diclofenac sodium, ibuprofen, piroxicam, flunixin and flunixin meglumine.

68. The method of claim 67 wherein the NSAID is diclofenac sodium.

20 69. The method of claim 61 or 63 wherein component (1) is an ant-cancer agent.

70. The method of any one of claims 61 to 69 wherein the pharmaceutical composition further comprises suitable topical excipients.

71. The method of claim 61 or 69 wherein the disease or condition is basal cell carcinoma.

25 72. The method of claim 61 or 69 wherein the disease or condition is actinic keratoses.

73. The method of claim 61 or 69 wherein the disease or condition is liver spots.

74. The method of claim 61 or 69 wherein the disease or condition is squamous cell tumours.

30 75. The method of claim 61 or 69 wherein the disease or condition is metastatic cancer of the breast to the skin.

76. The method of claim 61 or 69 wherein the disease or condition is primary and metastatic melanoma of the skin.

35 77. The method of claim 61 or 69 wherein the disease or condition is malignancies and/or tumour of the skin.

78. The method of claim 61 or 69 wherein the disease or condition is genital warts (condyloma acuminata).

79. The method of claim 61 or 69 wherein the disease or condition is cervical cancer.

80. The method of claim 61 or 69 wherein the disease or condition is Human Papilloma Virus (HPV).

81. The method of claim 61 or 69 wherein the disease or condition is psoriasis.

82. The method of claim 61 or 69 wherein the disease or condition is corns on the feet.

83. The method of claim 61 or 69 wherein the disease or condition is the hair loss on the head of pregnant women.

84. The method of any one of claims 61 or 69 wherein the administering takes place a number of times a day over a number of weeks.

85. Percutaneous delivery of a therapeutically effective dosage amount of a drug which inhibits prostaglandin synthesis said dosage amount taken from a pharmaceutical composition and applied to the skin or exposed tissue of a human, the drug being transported to the site of trauma or pathology, on or in the skin or exposed tissue of the human, to treat a disease or condition of the skin or exposed tissue, the delivery comprising topically administering to the skin or exposed tissue site of the trauma or pathology the therapeutically effective non-toxic dosage amount of the drug which inhibits prostaglandin synthesis in a composition which also comprises an effective non-toxic amount of hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons sufficient to transport the drug to the epidermis to the site of the trauma or pathology to block the synthesis of prostaglandin, wherein the amount of hyaluronic acid or salts thereof exceeds at least about 5mg/cm² of the skin or exposed tissue to which the composition is to be applied and wherein the concentration of the drug is 1-5% by weight and the concentration of the form of hyaluronic acid is 1-3% by weight of the composition.

86. The percutaneous delivery of claim 85 wherein the hyaluronic acid or salts thereof is sodium hyaluronate.

87. The percutaneous delivery of claim 85 or 86 wherein the molecular weight of the hyaluronic acid or salts is less than about 750,000 Daltons.

88. The percutaneous delivery of any one of claims 85 to 87 wherein the drug comprises an anti-cancer drug for administration to a tumor or malignancy in the skin or exposed tissue.

89. The percutaneous delivery of claim 88 wherein the drug is 10 mg of novantrone in the dosage amount of the composition and the hyaluronic acid or salts thereof in the dosage amount is in excess of about 5 mg of sodium hyaluronate per cm² of the skin or exposed

tissue, to which the dosage amount is applied for the percutaneous transport of the novantrone.

90. A method of treating a disease or condition selected from the group consisting of actinic keratoses, liver spots, squamous cell tumours, malignancies of the skin, genital warts, cervical cancer, Psoriasis, corns on the feet, and hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human a dosage amount of a pharmaceutical composition, said dosage amount consisting essentially of:

(1) an agent selected from a medicinal and therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof.

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such for that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated and wherein the form of hyaluronic acid has a molecular weight less than 750,000 Daltons and greater than 150,000 Daltons, said administrations continuing until such time as no longer required and wherein component (2) is between about 1% and about 3% by weight of the composition and wherein component (1) is between 1% and about 5% by weight of the composition.

91. The method of claim 90 wherein component (1) is a non-steroidal anti-inflammatory drug (NSAID).

92. The method of claim 90 or 91 wherein component (2) is sodium hyaluronate whose molecular weight is between 150,000 Daltons and 225,000 Daltons.

93. The method of claim 90 or 91 wherein the disease or condition is actinic keratoses.

94. The method of claim 90 or 91 wherein component (1) is a non-steroid anti-inflammatory drug selected from the group consisting of indomethacin, naproxen, (+/-) tromethamine, salt of ketorolac, ibuprofen, piroxicam, acetylsalicylic acid and flunixin.

95. The method of claim 90 or 91 wherein component (1) is a non-steroid anti-inflammatory drug selected from the group consisting of diclofenac and diclofenac sodium and wherein the form of hyaluronic acid is 2 1/2% by weight of the composition and the form of NSAID is 3% by weight of the composition.

96. The method of claim 90 or 91 wherein the malignancies of the skin is basal cell carcinoma.

97. The pharmaceutical composition of claim 1 wherein the disease or condition is pain and the amount of the form of hyaluronic acid is at least 10 mg/cm².

98. A method of treating pain topically, said method comprising administering topically to the skin or exposed tissue of a human a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a non-steroidal anti-inflammatory drug (NSAID) in a therapeutically effective amount to treat pain of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid, its non-toxic salts and combination thereof being between 1% and 3% by weight of the composition.

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of pain to be treated, in the skin or exposed tissue, and wherein the molecular weight of the form of hyaluronic acid is less than 750,000 Daltons.

99. The method of claim 98 wherein component (2) is sodium hyaluronate having a molecular weight less than 750,000 daltons.

100. The method of claim 98 or 99 wherein component (1) is between 1% to 5% by weight of the composition.

101. The method of claim 98 or 99 wherein the NSAID is diclofenac sodium.

102. The method of claim 99 wherein component (2) is sodium hyaluronate whose molecular weight is between 150,000 Daltons and 225,000 Daltons.

103. The method of claim 98 or 99 wherein the NSAID is selected from the group consisting of diclofenac sodium, ibuprofen, piroxicam, flunixin and flunixin meglumine.

104. The method of claim 98 or 99 wherein the pharmaceutical composition further comprises suitable topical excipients.

105. The method of claim 95 or 99 wherein the administering tasks place a number of times a day over a number of weeks.

106. A method of treating a mammal for a condition of the skin or exposed tissue selected from the group consisting of basal cell carcinoma and actinic keratoses, which method consists essentially of topically administering to the site of the condition, more than once per day over a period of days sufficient to treat the condition, a non-toxic effective dosage amount of a composition consisting essentially of

(a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis,

(b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site of the condition, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and 750,000 daltons, and

(c) a pharmaceutical excipient suitable for topical application.

107. The method of claim 106 wherein the treatment is applied for a period of weeks.

108. The method of claim 106 or 107 wherein the concentration of the NSAID is between 1-5% by weight of the composition.

109. The method of claim 106 or 107 wherein the NSAID is selected from the group consisting of diclofenac, diclofenac sodium, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac, ibuprofen, piroxicam, acetylsalicylic acid and flunixin and wherein the concentration of the NSAID is between 1%-5% by weight of the composition.

110. The method of claim 106 or 107 wherein the concentration of hyaluronic acid or salt thereof is 2 1/2% by weight of the composition and the concentration of NSAID is 3% by weight of the composition.

111. The method of claim 106 or 107 wherein the hyaluronic acid or salt thereof is sodium hyaluronate and is in the concentration of 2 1/2% by weight of the dosage amount and the NSAID is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount.

112. A method of treating a mammal for a condition of the skin or exposed tissue selected from the group consisting of basal cell carcinoma and actinic keratoses, which method consists essentially of topically administering to the site of the condition, more than once per day over a period of days sufficient to treat the condition, a non-toxic effective dosage amount of a composition consisting essentially of

(a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis, wherein the concentration of the NSAID between 1-5% by weight of the composition,

(b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site of the condition, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and 750,000 daltons, and

(c) a pharmaceutical excipient suitable for topical application.

113. The method of claim 112 wherein the treatment is applied for a period of weeks.

114. The method of claim 112 or 113 wherein the NSAID is selected from the group consisting of diclofenac, diclofenac sodium, indomethacin, naproxen, (+/-) tromethamine salt of ketorolac, ibuprofen, piroxicam, acetylsalicylic acid and flunixin.

5 115. The method of claim 112 or 113 wherein the hyaluronic acid or salt thereof is sodium hyaluronate in a concentration of 2 1/2% by weight of the composition and the NSAID is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount.

10 116. A method of treating a mammal for actinic keratosis of the skin or exposed tissue, which method consists essentially of topically administering to the site of the actinic keratosis, more than once per day over a period of days sufficient to treat the actinic keratosis, a non-toxic effective dosage amount of a composition consisting essentially of

(a) a non-steroidal anti-inflammatory drug (NSAID) in an amount sufficient to block prostaglandin synthesis,

15 (b) hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount effective to transport said NSAID into the skin or exposed tissue at the site of the actinic keratosis, wherein the concentration of the hyaluronic acid or salt thereof is between 1-3% by weight of the composition, and the molecular weight of the hyaluronic acid or salt thereof is between 150,000 and 750,000 daltons, and

20 (c) a pharmaceutical excipient suitable for topical application.

117. The method of claim 116 wherein the treatment is applied for a period of weeks.

118. The method of claim 117 wherein the percent of the NSAID in the composition is between 1-5% by weight of the composition.

25 119. The method of any one of claims 116 to 118 wherein the NSAID is selected from the group consisting of diclofenac, diclofenac sodium, indomethacin, naproxen, (+/-) tromethamine salt of ketorolac, ibuprofen, piroxicam, acetylsalicylic acid and flunixin.

30 120. The method of claim 116 wherein the hyaluronic acid or salt thereof is sodium hyaluronate having a molecular weight between 150,000 daltons and 750,000 daltons and is in the concentration of 2 1/2% by weight of the composition and the NSAID is diclofenac sodium and is in the concentration of 3% by weight of the composition.

121. The method of claim 120 wherein the pharmaceutical excipient comprises an effective amount of a solubilizer for the diclofenac sodium.

122. The method of claim 121 wherein the solubilizer is methoxypolyethylene glycol.

35 123. The method of claim 120 wherein the pharmaceutical excipient comprises sterile water and an effective solubilizing amount of methoxypolyethylene glycol 350 for the diclofenac sodium.

124. A pharmaceutical composition from which effective non-toxic dosage amounts may be taken and applied to the skin or exposed tissue of a human, each effective dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a non-steroidal anti-inflammatory drug to treat a disease or condition of the skin or exposed tissue of a human involving a pathology and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof sufficient to transport the drug percutaneously into the skin or exposed tissue to accumulate and remain in the epidermis for a prolonged period of time and which is systemic independent acting and wherein said pharmaceutical composition comprises 3% by weight of the drug and 2.5% by weight of the form of hyaluronic acid having a molecular weight less than 750,000 daltons and greater than 150,000 daltons.

125. The composition of Claim 124 wherein the form of hyaluronic acid is sodium hyaluronate and the molecular weight is in the order of 665,000 daltons.

126. The composition of Claim 124 or 125 wherein the disease or condition is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumorous, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies or tumours of the skin, genital warts, cervical cancer, Human Papilloma Virus, psoriasis, corns on the feet and hair loss on the head of pregnant women.

127. The composition of any one of Claims 124 to 126 wherein each of the dosage amounts that can be taken comprise an effective amount of the drug and an amount of the form of hyaluronic acid in excess of $5\text{mg}/\text{cm}^2$ of the skin or exposed tissue.

128. The composition of any one of Claims 124 to 127 wherein the form of hyaluronic acid is sodium hyaluronate and the molecular weight is in the order of 207,000 daltons.

129. The composition of any one of Claims 124 to 128 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

130. The composition of Claim 129 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

131. The composition of Claim 129 wherein the NSAID is selected from ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

132. The composition of any one of Claims 124 to 128 wherein the drug is an anti-cancer drug:

133. The composition of Claim 132 wherein the anti-cancer drug is selected from Novantrone and 5-Fu (FLUORACIL).

134. The composition of any one of Claims 124 to 129 wherein the composition is packaged in a container from which each of the effective dosage amounts is taken.

135. The composition of any one of Claims 124 to 129 wherein the composition is in a tube having a mouth of predetermined diameter from which the dosage amount of the composition is taken.

136. A composition comprising in gel or cream form suitable for topical application comprising: 3% by weight diclofenac, 2 $\frac{1}{2}$ % by weight hyaluronic acid or a salt thereof having a molecular weight less than about 750,000 Daltons, and greater than 150,000 Daltons, a solubilizer for solubilizing the diclofenac, and a preservative.

137. The composition of Claim 136 further comprising 5% by weight glycerine and 3% benzyl alcohol.

138. The composition of Claim 136 wherein the preservative is 1% benzyl alcohol and the solubilizer is 20% methoxypolyethylene glycol.

139. The composition of any one of Claims 136 to 138 further comprising a container for holding the composition.

140. The dosage amount of Claim 124 or 136 wherein the form of hyaluronic acid is sodium hyaluronate and the molecular weight is between 150,000 Daltons and 225,000 Daltons.

141. The dosage amount of Claim 124 wherein the non-steroidal anti-inflammatory drug (NSAID) is selected from the group consisting of diclofenac, diclofenac sodium, ibuprofen, piroxicam, flunixin and flunixin meglumine.

142. The dosage amount of Claim 124 wherein the pharmaceutical excipients comprises a solubilizer.

143. The dosage amount of Claim 142 wherein the solubilizer is methoxypolyethylene glycol 350.

144. The pharmaceutical composition of Claim 124 wherein each of the dosage amounts that can be taken comprise an effective amount of the drug and an amount of the form of hyaluronic acid in an amount of at least 10 mg/cm² of skin or exposed tissue to which it is to be applied.

145. The pharmaceutical composition of Claim 124 wherein each of the dosage amounts that can be taken comprise an effective amount of the drug and an amount of the form of hyaluronic acid in an amount of at least 20 mg/cm² of skin or exposed tissue to which it is to be applied.

146. A dosage amount of a pharmaceutical composition comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue involving a pathology; and

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof and combination thereof having a molecular weight less than 750,000 daltons and greater than 150,000 daltons,

characterized in that the dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and in a form immediately available to transport component (1) percutaneously into the epidermis of skin or exposed tissue to the site of trauma or pathology of the disease in the skin or exposed tissue to be treated on application to the skin or exposed tissue for accumulation in the epidermis before passage therefrom and wherein the concentration by weight of component (1) and the concentration by weight of component (2) are selected from one of the group consisting of:

(i) the concentration of component (2) equals 2.5% by weight of the dosage amount and component (1) is a non-steroidal anti-inflammatory drug (NSAID);

(ii) component (2) equals or is less than 3% by weight of the dosage amount but equals or exceeds 1% by weight and component (1) equals or exceeds 1% by weight of the dosage amount but is less than 5% by weight.

147. The dosage amount of Claim 146 wherein component (2) is sodium hyaluronate and is in the concentration of 2.5% by weight of the dosage amount and component (1) is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount.

148. The dosage amount of Claim 147 wherein component (2) is sodium hyaluronate and the molecular weight is in the order of 665,000 Daltons.

149. The dosage amount of Claim 148 wherein component (2) is sodium hyaluronate and the molecular weight is in the order of 207,000 Daltons.

150. The dosage amount of Claim 148 wherein component (2) is sodium hyaluronate and the molecular weight is between 150,000 Daltons and 225,000 Daltons.

151. The dosage amount of Claim 146 or 148 wherein component (1) is a non-steroidal anti-inflammatory drug (NSAID).

152. The dosage amount of Claim 151 wherein the NSAID is selected from diclofenac, diclofenac sodium, ibuprofen, piroxicam, flunixin and flunixin meglumine.

153. The dosage amount of Claim 146 wherein component (1) is an anti-cancer agent.

154. The dosage amount of Claim 148 further comprising suitable topical excipients.

155. The dosage amount of Claim 154 wherein the topical excipients comprises a solubilizer.

156. The dosage amount of Claim 155 wherein the solubilizer is methoxypolyethylene glycol 350.

157. The dosage amount of Claim 148 or 154 wherein component (2) is in an amount of at least 10 mg/cm² of skin or exposed tissue to which it is to be applied.

158. The dosage amount of Claim 148 or 154 wherein component (2) is in an amount of at least 20 mg/cm² of skin or exposed tissue to which it is to be applied.

5 159. A dosage amount of pharmaceutical composition suitable for controlling the unloading of a drug from the skin or exposed tissue of a human into the lymphatic system, the dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat disease in the lymphatic system in human and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the
10 group consisting of hyaluronic acid and salts thereof and combination thereof sufficient to control the unloading of the drug into the lymphatic system wherein the effective amount of the form of hyaluronic acid exceeds 5 mg/cm² of the skin or exposed tissue and the molecular weight of the form of hyaluronic acid is greater than 150,000 Daltons and less than 750,000 Daltons and wherein the form of hyaluronic acid present is between 1% to 3% by
15 weight of the dosage amount.

160. The dosage amount of Claim 124 wherein the form of hyaluronic acid is sodium hyaluronate being 2.5% by weight of dosage amount and the drug is between 1% to 5% by weight of the dosage amount and the drug is selected from an NSAID and an anti-cancer drug.

20 161. A dosage amount of pharmaceutical composition suitable for application to the skin or exposed tissue of a human, the dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic amount of a non-steroidal anti-inflammatory drug (NSAID) to treat pain of the skin and exposed tissue of a human and an effective non-toxic amount of a form of hyaluronic acid selected from the group consisting of
25 hyaluronic acid and salts thereof and combinations thereof sufficient to transport and facilitate the drug percutaneously into the epidermis of the skin or exposed tissue of the pain to be treated wherein the dosage amount of the composition accumulates and remains in the epidermis for a prolonged period of time and which is systemic independent acting and wherein the effective amount of the form of hyaluronic acid exceeds 10 mg/cm² of the skin
30 or exposed tissue and the molecular weight of the form of hyaluronic acid is greater than 150,000 Daltons and less than 750,000 Daltons.

162. A dosage amount of a pharmaceutical composition comprising:

(1) a therapeutically effective amount of a drug to treat a disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and combinations thereof having a molecular weight greater than 150,000 Daltons and less than 750,000 Daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom, and wherein the concentrations by weight of components (1) and (2) in the dosage amount are selected from the group consisting of:

(xii) component (2) equals 2.5% by weight of the dosage amount and component (1) equals 3% by weight of the dosage amount; and

(xiii) component (2) equals or is less than 3% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount and component (1) equals or is less than 5% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount.

163. The dosage amount of Claim 161 or 162 wherein the form of hyaluronic acid is sodium hyaluronate and wherein the drug is diclofenac or salts thereof.

164. A pharmaceutical composition from which an effective non-toxic dosage amounts are to be taken and applied topically to the skin or exposed tissue of a human, each effective dosage amount consisting essentially of pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat diseases and conditions of the skin or exposed tissue of a human and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, non-toxic salts thereof and combination thereof having a molecular weight less than 750,000 daltons and greater than 150,000 daltons sufficient to transport the drug percutaneously into the epidermis of the skin or exposed tissue of a site in need of treatment wherein the composition accumulates and remains in the epidermis for a prolonged period of time and which is systemic independent acting and wherein the drug in the pharmaceutical composition is between about 1% and about 5% by weight of the composition and the amount of the form of hyaluronic acid in the composition is between about 1% and about 3% by weight of the composition and wherein each dosage to be taken comprises a minimum of 5 mg of the form of hyaluronic acid per square centimeter of skin or exposed tissue to which it is to be applied.

165. The composition of claim 164 wherein the drug is a non-steroidal anti-inflammatory agent (NSAID) in an amount between about 1% and about 5% of the composition by weight and the pharmaceutical excipients include a preservative and a solubilizer for the NSAID.

166. The composition of claim 165 wherein the form of the composition is selected from the group consisting of a gel and cream suitable for topical application and wherein the NSAID is 3% by weight diclofenac, the form of hyaluronic acid is present as 2 1/2% by weight of the composition, and the pharmaceutical excipients include a solubilizer for solubilizing the diclofenac, and a preservative.

167. The composition of claim 166 wherein the preservative is benzyl alcohol present as 1% by weight of the composition and the solubilizer is methoxypolyethylene glycol present as 20% by weight of the composition.

168. The composition of claim 166 suitable for topical application wherein the pharmaceutical excipients include 20% by weight methoxypolyethylene glycol, 1% by weight benzyl alcohol, 3% by weight diclofenac sodium, 2.5% by weight sodium hyaluronate, and the balance is sterile water.

169. A composition comprising in a form suitable for administration to the skin or exposed tissue of a human comprising: an effective amount of a non-steroidal anti-inflammatory agent (NSAID) being between about 1% and about 5% of the composition by weight, an amount of hyaluronic acid or salts thereof being between about 1% and about 3% by weight of the composition, a preservative and a solubilizer if required and water, the composition being such that an effective dosage amount may be taken from the container and applied to the skin or exposed tissue wherein the hyaluronic acid or salts thereof rapidly transports the drug to a site of trauma or pathology in the skin or tissue to which the composition is applied and which accumulates there and remains there for a prolonged period of time and which composition is systemic independent acting.

170. A composition comprising in gel or cream form suitable for topical application, 3% by weight diclofenac, 2 1/2% by weight hyaluronic acid or a salt thereof having a molecular weight less than about 750,000 Daltons and greater than 150,000 Daltons, a solubilizer for solubilizing the diclofenac, and a preservative.

171. The composition of claim 170 further comprising 5% by weight glycerine and 3% benzyl alcohol.

172. The composition of claim 170 wherein the preservative is 1% benzyl alcohol and the solubilizer is 20% methoxypolyethylene glycol.

173. The composition of any one of claims 170 to 172 further comprising a container for holding the composition.

174. A dosage amount of a pharmaceutical composition consisting essentially of
(1) pharmaceutical excipients suitable for topical application including water;
(2) a therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and exposed tissue and;

5 (3) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-toxic salts thereof, having a molecular weight less than 750,000 daltons and greater than 150,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and exposed tissue, is in a dosage amount in which
10 component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (3) is immediately available to transport component (2) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged
15 period before passage therefrom, and wherein the concentrations by weight of components (2) and (3) in the dosage amount are selected from:

(i) component (3) equals or is less than 3% by weight of the dosage amount but equal to or greater than 1% by weight of the dosage amount and component (2) equals or is less than 5% by weight of the dosage amount but equal to or greater than 1% by weight of
20 the dosage amount, and

(ii) component (3) is about 2 1/2% by weight of the dosage amount and component (2) is 3% by weight of the dosage amount.

175. The dosage amount of claim 174 wherein the concentration of components (2) and (3) in the dosage amounts is that in subparagraph (i).

25 176. The dosage amount of claim 174 wherein the concentration of components (2) and (3) in the dosage amounts is that in subparagraph (ii).

177. The dosage amount of claim 175 wherein component (2) is an NSAID.

178. The dosage amount of claim 177 wherein component (2) is an NSAID.

179. The dosage amount of claim 177 wherein component (3) exceeds 10 mg/cm².

30 180. The dosage amount of claim 179 wherein component (3) exceeds 10 mg/cm².

181. The dosage amount of the pharmaceutical composition of any one of claims 174 to 180 wherein the disease or condition is selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical
35 cancer, Human Papilloma Virus, Psoriasis, corns on the feet, and hair loss on the head of pregnant women.

182. A method of treating a disease or condition in humans, the method comprising topically administering a pharmaceutical composition from which effective non-toxic dosage amounts may be taken and applied to the skin or exposed tissue of a human, each effective dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a drug to treat the disease or condition of the skin or exposed tissue of a human and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof sufficient to transport the drug, to a site in the skin including epidermis or exposed tissue of the disease or condition for percutaneous transport into the skin or exposed tissue to accumulate and remain there for a prolonged period of time and which is systemic independent acting and wherein the concentration of the drug is 3% by weight and the concentration of the form of hyaluronic acid is 2.5% by weight having a molecular weight less than 750,000 daltons and greater than 150,000 daltons and wherein the dosage amount of the form of hyaluronic acid exceeds 5mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied.

183. A method of treating a disease or condition selected from the group consisting of basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus, Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, wherein the concentration of component (1) is between 1% and 5% by weight of the composition and the concentration of component (2) is between 1%

and 3% having a molecular weight less than 750,000 daltons and greater than 150,000 daltons.

184. The method of Claim 182 or 183 wherein the form of hyaluronic acid is sodium hyaluronate.

5 185. The method of Claim 183 or 184 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID) selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac, Ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

10 186. The method of Claim 183 wherein component (2) is sodium hyaluronate and is in the concentration of 2¹/₂% by weight of the dosage amount, component (1) is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount, and said dosage amount further comprises a solubilizer for solubilizing the diclofenac, and a preservative.

187. The method of Claim 184 wherein the disease or condition is basal cell carcinoma.

15 188. The method of Claim 184 wherein the disease or condition is actinic keratosis lesions.

189. The method of Claim 184 wherein the disease or condition is liver spots.

190. The method of Claim 184 wherein the disease or condition is squamous cells tumours.

20 191. The method of Claim 184 wherein the disease or condition is metastatic cancer of the breast to the skin.

192. The method of Claim 184 wherein the disease or condition is metastatic melanoma in the skin.

25 193. The method of Claim 184 wherein the disease or condition is malignancies and/or tumours of the skin.

194. The method of Claim 184 wherein the disease or condition is genital warts.

195. The method of Claim 184 wherein the disease or condition is cervical cancer.

196. The method of Claim 184 wherein the disease or condition is HPV (Human Papilloma Virus) including HPV of the cervix.

30 197. The method of Claim 184 wherein the disease or condition is psoriasis (both plaque type psoriasis and nail bed psoriasis).

198. The method of Claim 184 wherein the disease or condition is corns on the feet.

199. The method of Claim 184 wherein the disease or condition is hair loss on the head of pregnant women.

200. A method of ~~treating actinic keratoses~~, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat the disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-toxic salts thereof, and combination thereof having a molecular weight in the range of 150,000 to 750,000 daltons,

said dosage amount of said composition is in a dosage form suitable for topical application to the skin and/or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

201. The method of Claim 200 wherein the molecular weight of the form of hyaluronic acid is 665,000 daltons.

202. The method of Claim 201 wherein the form of hyaluronic acid is sodium hyaluronate.

203. The method of Claim 200 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight of 225,000 daltons.

204. The method of any one of Claims 200 to 203 wherein the agent is a non-steroidal anti-inflammatory drug (NSAID).

205. The method of any one of Claims 200 to 204 wherein the agent is an NSAID and the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac, ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

206. The method of Claim 200 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight of 207,000 daltons.

207. A method of rapidly transporting a drug to the epidermis and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective non-toxic dosage amount of a drug to treat a disease or condition of the skin or exposed tissue and an amount exceeding 5 mg/cm^2 of the skin or exposed tissue of hyaluronic acid or salts thereof having a molecular weight greater

than 150,000 daltons and less than 750,000 daltons to facilitate the rapid transport of the drug to the site in the skin or tissue of the disease or condition to the site of the pathology or trauma to accumulate there and be retained there for a prolonged period of time.

5 208. The method of claim 207 wherein the hyaluronic acid or salts thereof is sodium hyaluronate.

209. The method of claim 207 or 208 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

210. The method of claim 207 or 208 wherein the drug is an anti-cancer drug.

10 211. The method of claim 209 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

212. The method of claim 210 wherein the drug is selected from Novantrone and 5-Fu (FLUORACIL).

213. The method of claim 211 wherein the NSAID is selected from ibuprofen, piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

15 214. The method of claim 207 or 208 wherein the form of hyaluronic acid is in excess of 10mg per cm² and has a molecular weight less than about 750,000 Daltons.

20 215. A method of accumulating a drug in the skin or exposed tissue of a human suffering from trauma or a pathology comprising topically administering to the skin or exposed tissue a composition comprising the drug and an effective non-toxic amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons comprising hyaluronic acid and non-toxic salts thereof to transport the drug into the skin or exposed tissue wherein the amount of the form of hyaluronic acid exceeds at least about 5 mg/cm² of the surface area of the skin or exposed tissue to which the composition is applied.

25 216. The method of claim 215 wherein the form of hyaluronic acid is sodium hyaluronate.

217. The method of claim 216 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight less than 225,000 Daltons and greater than 150,000 Daltons.

30 218. The method of claim 217 wherein the drug is a drug which inhibits prostaglandin synthesis.

219. The method of claim 217 wherein the drug is a non-steroidal anti-inflammatory drug.

35 220. The method of claim 219 wherein the drug is selected from diclofenac, indomethacin, naproxen and (+/-) tromethamine salt of ketorolac.

221. The method of claim 219 wherein the drug is selected from piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

222. A method of treating a disease or condition selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus, Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a medicinal or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin or exposed tissue and;

(2) a form of hyaluronic acid selected from hyaluronic acid and non-toxic salts thereof,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm² of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom wherein component (1) is between 1% and 5% by weight of the composition and component (2) is between 1% and 5% weight of the composition and has a molecular weight less than 750,000 daltons and greater than 150,000 Daltons.

223. The method of claim 222 wherein component (2) is between 1% to 3% by weight of the composition of sodium hyaluronic acid and component (1) is between 1% and 5% by weight of the composition of an NSAID and the balance is selected from excipients suitable for topical application and water.

224. The method of claim 222 wherein the hyaluronic acid or salt thereof is sodium hyaluronate.

225. The method of claim 222 wherein component (1) is 3% by weight diclofenac or diclofenac sodium and component (2) is 2 1/2% by weight sodium hyaluronate.

226. The method of claim 222 or 224 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

227. The method of any one of claims 202 to 226 wherein the drug is an NSAID and the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

228. A method of accumulating a drug and a form of hyaluronic acid in the skin or exposed tissue or both comprising topically administering a dosage of a pharmaceutical composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective to treat and resolve a disease or condition of the skin and exposed tissue, selected from the group consisting of basal cell carcinoma and actinic keratoses, and pain non-toxic to the patient amount of a drug and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and non-toxic salts thereof sufficient to facilitate the drug's quick penetration to the site in the skin or tissue of the disease or condition to accumulate and remain there for a prolonged period of time wherein the percentage of the dosage of the form of the hyaluronic acid is between 1% and 3% by weight of the dosage and has a molecular weight less than 750,000 Daltons and greater than 150,000 daltons and the percent of the drug of the composition is between 1% and 5% by weight of the dosage.

229. The method of claim 228 wherein the form of hyaluronic acid is sodium hyaluronate and the dosage is 20 mg/cm².

230. A method of quickly delivering a drug to the epidermis and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a dosage of a pharmaceutical composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective, to treat and resolve a disease a condition of the skin and exposed tissue, selected from the group consisting of basal cell carcinoma and actinic keratoses, non-toxic to the patient amount of a drug which blocks prostaglandin synthesis and an amount of a form of hyaluronic acid selected from hyaluronic acid non-toxic salts thereof sufficient to facilitate the drug's quick penetration to the site in the skin or tissue of the disease or condition through the tissue to accumulate and remain there for an prolonged period of time to block prostaglandin synthesis wherein the percentage of the dosage of the form of the hyaluronic acid is between 1% and 3% by weight of the dosage and has a molecular weight less than 750,000 daltons and greater than 150,000 daltons and the percent of the drug of the composition is between 1% and 5% by weight of the dosage.

231. The method of claim 230 wherein accumulation takes place in the epidermis.

232. The method of claim 230 wherein the form of hyaluronic acid dosage is 20 mg/cm².

233. The method of claim 231 wherein the form of hyaluronic acid is in an amount between 30 mg and 60 mg.

234. A method of treating pain topically, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:

(1) a non-steroidal anti-inflammatory drug (NSAID) in a therapeutically effective amount to treat pain of the skin or exposed tissue and;

(2) hyaluronic acid or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of pain to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

235. The method of claim 234 wherein component (2) is sodium hyaluronate.

236. The method of claim 234 or 235 wherein component (1) is diclofenac.

237. The method of claim 235 wherein the NSAID is diclofenac sodium.

238. The method of claim 234 wherein component (2) is sodium hyaluronate and is in the concentration of $2\frac{1}{2}\%$ by weight of the dosage amount, component (1) is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount, and said dosage amount further comprises a solubilizer for solubilizing the diclofenac, and a preservative.

239. A method of accumulating a medicine or therapeutic agent (component (1)) and a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons (component (2)) in the epidermis of the skin or exposed tissue of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a pharmaceutical composition comprising components (1) and (2) characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, and wherein the pharmaceutical composition further comprising pharmaceutical excipients suitable for topical application.

240. The method of any one of claim 239 wherein the form of hyaluronic acid is sodium hyaluronate.

241. A method of rapidly transporting a drug to the epidermis and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective non-toxic dosage amount of a drug to treat a disease or condition of the skin or exposed tissue at the site the trauma or pathology, and an amount of hyaluronic acid or salts thereof to facilitate the rapid transport of the drug to the site in the skin or tissue of the disease or condition to accumulate there and be retained there for a prolonged period of time and wherein the form of hyaluronic acid is administered in excess of 5 mg/cm² having a molecular weight greater than 150,000 daltons and less than 750,000 daltons.

242. The method of claim 241 wherein the hyaluronic acid or salts thereof is sodium hyaluronate.

243. The method of claim 241 or 242 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

244. The method of claim 241 or 242 wherein the drug is an anti-cancer drug.

245. The method of claim 243 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (±) tromethamine salt of ketorolac.

246. The method of claim 244 wherein the drug is selected from Novantrone and 5-Fu (FLUORACIL).

247. The method of claim 243 wherein the NSAID is selected from ibuprofen, piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

248. A method of controlling the unloading of a drug from the skin or exposed tissue of a human suffering trauma or pathology into the lymphatic system comprising: delivering an amount of drug into the skin or exposed tissue by an effective non-toxic dosage amount of a form of hyaluronic acid selected from units of hyaluronic acid and salts thereof to the skin or exposed tissue wherein the amount of a form of hyaluronic acid exceeds at least about 5 mg/cm² having a molecular weight greater than 750,000 Daltons and less than 150,000 Daltons.

249. The method of claim 248 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight less than about 225,000 Daltons.

250. The method of claim 248 or 249 wherein the drug is a drug which inhibits prostaglandin synthesis.

251. The method of claim 250 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

252. The method of claim 250 wherein the drug is selected from diclofenac, indomethacin, naproxen and (\pm) tromethamine salt of ketorolac.

253. The method of claim 250 wherein the drug is selected from ibuprofen, piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

5 254. A method of accumulating a drug and a form of hyaluronic acid in the skin of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable for topical applications, an effective non-toxic dosage amount of a drug which inhibits prostaglandin synthesis to treat a disease or condition of the skin involving pathological tissue or underperfused tissue and an
10 effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof effective to transport the drug percutaneously to the site in the epidermis of the skin of the disease or condition to accumulate and remain at the site in the skin or exposed tissue for a prolonged period of time before passage therefrom, wherein the amount of the form of
15 hyaluronic acid administered is at least 5 mg/cm² of skin having a molecular weight of less than 750,000 daltons and greater than 150,000 daltons.

255. The method of Claim 254 where the accumulation takes place in the epidermis.

256. The method of Claim 254 wherein the form of hyaluronic acid is sodium
20 hyaluronate having 1-3% by weight of the composition and the percent of the drug in the composition is 1-5% by weight.

257. A method of accumulating a medicine or therapeutic agent which inhibits prostaglandin synthesis (component (1)) and a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and combination thereof, having a
25 molecular weight of less than 750,000 daltons and greater than 150,000 daltons (component (2)) in the epidermis of the skin of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a pharmaceutical composition comprising components (1) and (2) characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and in a dosage
30 amount in which component (2) exceeds 5 mg/cm² of the skin to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin to the site of trauma or pathology of the disease or condition to be treated in the skin, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, and wherein the pharmaceutical composition further comprises pharmaceutical
35 excipients suitable for topical application.

258. The method of Claim 257 wherein the form of hyaluronic acid is sodium hyaluronate being 1-3% by weight of the composition and the percent of the drug in the composition is 1-5% by weight.

259. A method of accumulating a drug in the skin or exposed tissue of a human suffering from trauma or a pathology comprising topically administering to the skin or exposed tissue a composition comprising the drug which inhibits prostaglandin synthesis and an effective non-toxic amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, salts thereof and combination thereof, having a molecular weight of less than 750,000 daltons and greater than 150,000 daltons to transport the drug into the skin wherein the amount of the form of hyaluronic acid exceeds at least about 10mg/cm² of the surface area of the skin to which the composition is applied.

260. The method of Claim 259 wherein the form of hyaluronic acid is sodium hyaluronate being 1-3% by weight of the composition and the percent of the drug in the composition is 1-5% by weight.

261. The method of Claim 260 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons and greater than 225,000 daltons and the drug is a non-steroidal anti-inflammatory drug (NSAID).

262. The method of Claim 257 or 259 wherein the drug is diclofenac.

263. A pharmaceutical composition from which effective non-toxic dosage amounts may be taken and applied to the skin or exposed tissue of a human, each effective dosage amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a non-steroidal anti-inflammatory drug to treat a disease or condition of the skin or exposed tissue of a human involving a pathology and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and its non-toxic salts and combination thereof sufficient to transport the drug percutaneously into the skin or exposed tissue to accumulate and remain in the epidermis for a prolonged period of time and which is systemic independent acting and wherein said pharmaceutical composition, substantially as hereinbefore described with reference to any one of Formulas 1 to 9.

264. A method of treating a disease or condition selected from the group consisting of basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies or tumour of the skin, genital warts, cervical cancer, Human Papilloma Virus, Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin or exposed tissue of a human, a dosage amount of a pharmaceutical composition of claim 140 in an amount which effectively treats said disease and/or condition.

265. A method of rapidly transporting a drug to the epidermis and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a therapeutically effective non-toxic dosage amount of a composition of claim 263 to treat a disease or condition of the skin or exposed tissue.

1. A pharmaceutical composition comprising a plurality of effective non-toxic dosage amounts of a composition for topical administration to the site of pathology and/or trauma of skin and/or exposed tissue of a human patient in need of treatment suffering from a disease or condition, each such dosage amount comprising a therapeutically effective non-toxic (to the patient) dosage amount of a drug for the treatment of the disease and/or condition of the skin and/or exposed tissue at the site of the pathology and/or trauma and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid to transport (to facilitate or cause the transport of) the drug to the site of the pathology and/or trauma of the disease or condition.

2. The pharmaceutical composition of Claim 1, wherein each of the plurality of effective non-toxic dosage amounts of the composition making up the pharmaceutical composition comprises at least about 5-10mg of the form of hyaluronic acid per cm² of the skin and/or exposed tissue to which the composition is to be applied.

3. The pharmaceutical composition of Claim 1 or 2 wherein the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid is hyaluronic acid and/or a salt thereof.

4. The pharmaceutical composition of Claim 1, 2 or 3 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.
5. The pharmaceutical composition of Claim 1, 2, 3 or 4 wherein the disease and/or condition of the skin and/or exposed tissue at the site of the trauma and/or pathology is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women.
6. The pharmaceutical composition of Claim 1, 2, 3, 4 or 5 wherein the drug comprises an effective non-toxic dosage amount which inhibits prostaglandin synthesis.
7. The pharmaceutical composition of Claim 6 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).
8. The pharmaceutical composition of Claim 1, 2, 3, 4 or 5 wherein the drug is an anti-cancer drug.
9. The pharmaceutical composition of Claim 8 wherein the anti-cancer drug is selected from novantrone.
10. The pharmaceutical composition of Claim 7 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.
11. The pharmaceutical composition of Claim 7 wherein the NSAID is selected from IBUPROFEN, PIROXICAM, Propionic Acid derivatives, acetylsalicylic acid and Flunixin.

12. A topically applicable percutaneous (intracutaneous) penetrating (best targeting the epidermis) systemic independent acting (not acting essentially through the blood) pharmaceutical composition comprising a plurality of dosage amounts, each dosage amount comprising, pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and to assist to resolve a disease and/or condition of the skin and exposed tissue, selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin primary and metastatic melanoma in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women, non-toxic (to the patient) dosage amount of a non-steroidal anti-inflammatory drug (NSAID) selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac and an effective non-toxic amount of hyaluronic acid and/or salts thereof to facilitate or cause the NSAID's rapid transport by the form of the hyaluronic acid to the site in the skin including the epidermis or exposed tissue of the disease or condition into the tissue to remain there for a prolonged period of time to assist to treat and assist to resolve the disease or condition by blocking prostaglandin synthesis.

13. The pharmaceutical composition of Claim 12 wherein the effective non-toxic dosage amount of the hyaluronic acid and/or salts thereof to transport the drug into the skin and/or exposed tissue exceeds about 5 mg. - 10 mg. for each 1 cm² of skin or exposed tissue area of the disease or condition to which the dosage amount is to be applied.

14. The pharmaceutical composition of Claim 13 wherein the molecular weight of the hyaluronic acid and/or salts is less than about 750,000 daltons.

18. The pharmaceutical composition of Claim 15, 16 or 17, wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.
19. The pharmaceutical composition of Claim 15, 16, 17 or 18 wherein the medicinal and/or therapeutic agent is a non-steroidal anti-inflammatory drug (NSAID).
20. A pharmaceutical composition comprising:
 (1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat disease or condition of the skin and/or exposed tissue;
 and (2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid,
 characterized in that said composition
 (a) is in a dosage form which is suitable for administration to skin and/or exposed tissue;
 and (b) is in such an amount and in such form that
 (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site of the skin or exposed tissue to be treated, and (ii) component (2) is immediately available to transport (facilitate or cause the transport of) component (1) to the site of trauma and/or pathology of the disease or condition to be treated, percutaneously into the skin or exposed tissue where the composition resides and accumulates for a prolonged period, and which component (2) is in an effective non-toxic dosage amount to transport (facilitate or cause the transport of) component (1) upon administration, percutaneously into the skin or exposed tissue to the site of the trauma and/or pathology.
21. The composition of Claim 20 wherein the form of hyaluronic acid in the composition comprises hyaluronic acid and/or salts thereof.
22. The composition of Claim 20 or 21 wherein the effective amount of the form of hyaluronic acid in the

18. The pharmaceutical composition of Claim 15, 16 or 17, wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.

19. The pharmaceutical composition of Claim 15, 16, 17 or 18 wherein the medicinal and/or therapeutic agent is a non-steroidal anti-inflammatory drug (NSAID).

20. A pharmaceutical composition comprising:

(1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat disease or condition of the skin and/or exposed tissue;

and (2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid,

characterized in that said composition

(a) is in a dosage form which is suitable for administration to skin and/or exposed tissue;

and (b) is in such an amount and in such form that (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site of the skin or exposed tissue to be treated, and (ii) component (2) is immediately available to transport (facilitate or cause the transport of) component (1) to the site of trauma and/or pathology of the disease or condition to be treated, percutaneously into the skin or exposed tissue where the composition resides and accumulates for a prolonged period, and which component (2) is in an effective non-toxic dosage amount to transport (facilitate or cause the transport of) component (1) upon administration, percutaneously into the skin or exposed tissue to the site of the trauma and/or pathology.

21. The composition of Claim 20 wherein the form of hyaluronic acid in the composition comprises hyaluronic acid and/or salts thereof.

22. The composition of Claim 20 or 21 wherein the effective amount of the form of hyaluronic acid in the

27. The use of Claim 26 wherein component (2) is hyaluronic acid and/or salts thereof having a molecular weight less than about 750,000 daltons.

28. The use of Claim 26 or 27 wherein the dosage amount of component (2) in the amount of the composition taken from the composition (to be taken from the composition) and applied to the skin and/or exposed tissue is present in a dose amount greater than about 5-10 mg per cm² of skin or exposed tissue to which the dosage amount is to be applied.

29. The use of Claim 26, 27 or 28 wherein component (1) is a non-steroidal anti-inflammatory drug (NSAID).

30. The use of:

(1) a medicinal and/or therapeutic agent which inhibits prostaglandin synthesis,

and (2) hyaluronic acid and/or salts thereof,

in the manufacture of a pharmaceutical composition for treating disease or condition at the site of trauma and/or pathology of the skin and exposed tissue in a therapy wherein a dosage amount comprises a therapeutically effective amount of said medicinal and/or therapeutic agent and a therapeutically effective amount of the hyaluronic acid and/or salts thereof having a molecular weight less than about 750,000 daltons, the use being characterized in that the amount of component (2) is immediately available to transport component (1) percutaneously into the epidermis at the site of the skin or exposed tissue to be treated and component (2) is an effective non-toxic amount to transport (facilitate the transport) of component (1) into the skin or exposed tissue.

31. The use of Claim 30 wherein the dosage amount of component (2) is present in a dose greater than 5-10 mg per cm² of skin or exposed tissue to which the composition is to be applied.

32. The pharmaceutical composition of Claim 20, 21, 22, 23, 24, or 25 include pharmaceutically compatible excipients

27. The use of Claim 26 wherein component (2) is hyaluronic acid and/or salts thereof having a molecular weight less than about 750,000 daltons.

28. The use of Claim 26 or 27 wherein the dosage amount of component (2) in the amount of the composition taken from the composition (to be taken from the composition) and applied to the skin and/or exposed tissue is present in a dose amount greater than about 5-10 mg per cm² of skin or exposed tissue to which the dosage amount is to be applied.

29. The use of Claim 26, 27 or 28 wherein component (1) is a non-steroidal anti-inflammatory drug (NSAID).

30. The use of:

(1) a medicinal and/or therapeutic agent which inhibits prostaglandin synthesis,

and (2) hyaluronic acid and/or salts thereof, in the manufacture of a pharmaceutical composition for treating disease or condition at the site of trauma and/or pathology of the skin and exposed tissue in a therapy wherein a dosage amount comprises a therapeutically effective amount of said medicinal and/or therapeutic agent and a therapeutically effective amount of the hyaluronic acid and/or salts thereof having a molecular weight less than about 750,000 daltons, the use being characterized in that the amount of component (2) is immediately available to transport component (1) percutaneously into the epidermis at the site of the skin or exposed tissue to be treated and component (2) is an effective non-toxic amount to transport (facilitate the transport) of component (1) into the skin or exposed tissue.

31. The use of Claim 30 wherein the dosage amount of component (2) is present in a dose greater than 5-10 mg per cm² of skin or exposed tissue to which the composition is to be applied.

32. The pharmaceutical composition of Claim 20, 21, 22, 23, 24, or 25 include pharmaceutically compatible excipients

39. The method of Claim 36, 37 or 38 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.
40. The method of Claim 36, 37, 38 or 39 wherein the treatment is applied daily for a number of weeks.
41. The method of Claim 36, 37, 38, 39 or 40 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).
42. The method of Claim 41 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.
43. The method of Claim 41 wherein the NSAID is selected from IBUPROFEN, PIROXICAM, Propionic Acid derivatives, acetylsalicylic acid and Flunixin.
44. The method of treatment of Claim 41, 42 or 43 wherein the treatment comprises applying effective dosage amounts of the composition, a number of times daily for a period of weeks to clear the trauma or pathology.
45. A container containing compositions for topical application to the skin and/or exposed tissue of a human comprising a plurality of dosage amounts of each of (a) a drug and (b) hyaluronic acid and/or sodium hyaluronate, each dosage amount comprising an effective non-toxic dosage amount of the drug to treat a disease and/or condition of the skin and an effective non-toxic dosage amount of hyaluronic acid and/or sodium hyaluronate to transport the drug into the skin and/or exposed tissue to the site of the pathology and/or trauma.
46. The container of Claim 45 wherein the hyaluronic acid and/or sodium hyaluronate has a molecular weight less than about 750,000 daltons to transport the drug into the skin and/or exposed tissue.

47. The container of Claim 45 wherein the effective dosage amount of the hyaluronic acid and/or sodium hyaluronate is in a dosage amount exceeding $5\text{mg}/\text{cm}^2$ of the hyaluronic acid and/or sodium hyaluronate in the dosage amount discharged.
48. The container of Claim 45, 46 or 47 wherein means are provided to assist the removal from the container of an effective dosage amount of the composition in the container for use to apply to the skin or exposed tissue at the site of trauma and/or pathology to treat the disease and/or condition.
49. The container of Claim 48 wherein the container is a tube and said means comprises a mouth opening of the tube to assist in the discharge of an effective dosage amount for discharge from the tube.
50. Percutaneous (intercutaneous) delivery of a therapeutically effective dosage amount of a drug and which inhibits prostaglandin synthesis in a pharmaceutical composition the drug being transported to the site of, on, or in the skin and/or exposed tissue of a human of trauma and/or pathology to treat a disease or condition of the skin and/or exposed tissue, the delivery comprising topically administering to the skin and/or exposed tissue site of the trauma and/or pathology, the therapeutically effective, non-toxic (to the patient) dosage amount of the drug which inhibits prostaglandin synthesis, in a composition which comprises an effective non-toxic amount of hyaluronic acid and/or salts thereof sufficient to transport, (facilitate or cause the transport of), the drug to the epidermis to the site of the trauma and/or pathology to block the synthesis of prostaglandins.
51. The percutaneous delivery of Claim 50 wherein the amount of hyaluronic acid and/or salts thereof exceeds at least about $5\text{mg}/\text{cm}^2$ of the skin and/or exposed tissue to which the composition is to be applied.

52. The percutaneous delivery of Claim 50 or 51 wherein the molecular weight of the hyaluronic acid and/or salts is less than about 750,000 daltons.

53. The percutaneous delivery of Claim 50, 51 or 52 wherein the drug comprises an anti-cancer drug for administration to a tumour or malignancy in the skin and/or exposed tissue.

54. The percutaneous delivery of Claim 53 wherein the drug is 10 mg of novantrone in the dosage amount of the composition and the hyaluronic acid and/or salts thereof is in excess of about 5 mg of sodium hyaluronic per cm^2 of the skin or exposed tissue, about 2.5% of the composition, for the percutaneous transport of the novantrone.

55. Use of a pharmaceutical composition to treat a disease or condition by the application of the composition to the skin and/or exposed tissue of a human, the amount of the composition, administered comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective non-toxic (to a human) amount of a drug which inhibits prostaglandin synthesis and an effective non-toxic dosage amount of at least about $5\text{mg}/\text{cm}^2$ of skin and/or exposed tissue of hyaluronic acid and/or salts thereof having a molecular weight less than about 750,000 daltons effective to transport the drug (to facilitate or cause the transport of the drug) percutaneously into the skin especially the epidermis at the site of the disease or condition to be treated, thereby blocking prostaglandin synthesis to enable the macrophages (and N.K. cells) to resolve the disease or condition.

56. A method of abating pain in skin and exposed tissue of a human suffering from a disease or condition comprising administering a composition comprising an effective non-toxic dosage amount of a drug which relieves pain and an effective non-toxic dosage amount of the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes.

esters, fragments, and/or subunits of hyaluronic acid in an amount exceeding 10-20 mg. per square cm (cm²) of the skin or exposed tissue to which it is applied for percutaneous transport of the drug by the form of hyaluronic acid into the epidermis proximate the paccinian nerve bundles to give pain relief.

57. The method of abating pain of Claim 56 wherein the form of hyaluronic acid is hyaluronic acid and/or salts thereof.

58. The method of abating pain of Claim 56 or 57 wherein the drug is an NSAID.

59. The method of Claim 56, 57 or 58 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.

60. A composition from which dosage amounts may be taken and applied to human skin and/or exposed tissue suffering pain for abating the pain, the composition comprising a plurality of dosage amounts which may be taken and applied, each dosage amount comprising an effective non-toxic dosage amount of an NSAID and an effective non-toxic dosage amount of the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or subunits of hyaluronic acid exceeding 10-20 mg. per square cm (cm²) of skin and/or exposed tissue to which it is applied, for percutaneous transport of the NSAID by the form of hyaluronic acid into the epidermis proximate the paccinian nerve bundles (superficial nerve bundles at the end of the nerves) to abate the pain.

61. The composition of Claim 60 wherein the form of hyaluronic acid is hyaluronic acid is hyaluronic acid and/or salts thereof.

62. The composition of Claim 60 or 61 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.

63. The composition of Claim 60, 61, or 62 in a container including means for assisting the discharge of an effective dosage amount from the container.

64. The composition of Claim 63 wherein the container is a tube and said means comprises a mouth opening of predetermined diameter through which the effective dosage amount of the composition is discharged.

1. The use of:

(1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and/or exposed tissue and;

(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and subunits of hyaluronic acid,

for the manufacture of a pharmaceutical composition for the topical treatment of said disease or condition of the skin and/or exposed tissue characterized in that said composition is applied in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom.

2. The use of Claim 1 wherein the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid is hyaluronic acid or a salt thereof.

3. The use of Claim 1 wherein the hyaluronic acid or salt thereof is sodium hyaluronate.

4. The use of Claim 1, 2 or 3 wherein the disease and/or condition is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin, genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women.
5. The use of Claim 1, 2, 3, 4 or 4 wherein the molecular weight of the form of hyaluronic acid is less than about 750,000 daltons.
6. The use of Claim 1, 2, 3, 4 or 5 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).
7. The use of Claim 6 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.
8. The use of Claim 6 wherein the NSAID is selected from Ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.
9. The use of Claim 1, 2, 3, 4 or 5 wherein the drug is an anti-cancer drug.
10. The use of Claim 9 wherein the anti-cancer drug is selected from Novantrone and 5-Fu (FLUORACIL).

11. The use of Claim 1, 2, 3, 4, 5 or 6 wherein the composition is packaged in a container from which each dosage amount is taken.
12. The use of Claim 1, 2, 3, 4, 5 or 6 wherein the composition is in a tube having a mouth of predetermined diameter from which the dosage amount of the composition is taken.
13. The use of Claim 1, 3 or 5 wherein the composition comprises in gel or cream form suitable for topical application, 3% by weight diclofenac, 2¹/₂% by weight hyaluronic acid and/or a salt thereof having a molecular weight less than about 750,000 daltons, a solubilizer for solubilizing the diclofenac, and a preservative.
14. The use of Claim 13 further comprising 5% by weight glycerine and 3% benzyl alcohol.
15. The use of Claim 13 wherein the preservative is benzyl alcohol (1%) and the solubilizer is methoxypolyethylene glycol (20%).
16. The use of Claim 13, 14 or 15 further comprising a container for holding the composition.
17. A use of Claim 1, 3 or 5 wherein the composition comprises glycerine (5% by weight), benzyl alcohol (3% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight), and sterile water (the balance) in a container.
18. The use of Claim 1, 3 or 5 wherein the composition comprises

methoxypolyethylene glycol (20% by weight), benzyl alcohol (1% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight), and sterile water (the balance) in a container.

19. The use of Claim 4, 5 or 6 wherein the disease and/or condition is basal cell carcinoma.
20. The use of Claim 4, 5 or 6 wherein the disease and/or condition is actinic keratosis lesions.
21. The use of Claim 4, 5 or 6 wherein the disease and/or condition is liver spots.
22. The use of Claim 4, 5 or 6 wherein the disease and/or condition is squamous cells tumours.
23. The use of Claim 4, 5 or 6 wherein the disease and/or condition is metastatic cancer of the breast to the skin.
24. The use of Claim 4, 5 or 6 wherein the disease and/or condition is metastatic melanoma in the skin.
25. The use of Claim 4, 5 or 6 wherein the disease and/or condition is malignancies and/or tumours of the skin.
26. The use of Claim 4, 5 or 6 wherein the disease and/or condition is genital warts.

27. The use of Claim 4, 5 or 6 wherein the disease and/or condition is cervical cancer.
28. The use of Claim 4, 5 or 6 wherein the disease and/or condition HPV (Human Papilloma Virus) including HPV of the cervix.
29. The use of Claim 4, 5 or 6 wherein the disease and/or condition is psoriasis (both plaque type psoriasis and nail bed psoriasis).
30. The use of Claim 4, 5 or 6 wherein the disease and/or condition is corns on the feet.
31. The use of Claim 4, 5 or 6 wherein the disease and/or condition is hair loss on the head of pregnant women.
32. A composition comprising in a form suitable for administration to the skin and/or exposed tissue of a human, an effective amount of a non-steroidal anti-inflammatory agent (NSAID), being between about 1% and about 5% of the composition by weight and an amount of hyaluronic acid and/or salts thereof being between about 1% and about 3% by weight of the composition, a preservative and a solubilizer if required and water, the composition being such that an effective dosage amount may be taken from the container and applied to the skin and/or exposed tissue wherein the hyaluronic acid rapidly transports the drug to a site of trauma and/or pathology in the skin and/or tissue to which the composition is applied and which accumulates there and remains there for a prolonged period of time and which composition is systemic independent acting.

33. The composition of Claim 32 further comprising the compositions being in a container.
34. A composition comprising in gel or cream form suitable for topical application, 3% by weight diclofenac, 2 1/2% by weight hyaluronic acid and/or a salt thereof having a molecular weight less than about 750,000 daltons, a solubilizer for solubilizing the diclofenac, and a preservative.
35. The composition of Claim 34 further comprising 5% by weight glycerine and 3% benzyl alcohol.
36. The composition of Claim 34 wherein the preservative is benzyl alcohol (1%) and the solubilizer is methoxypolyethylene glycol (20%).
37. The composition of Claim 34, 35 or 36 further comprising a container for holding the composition.
38. A composition suitable for topical application comprising glycerine (5% by weight), benzyl alcohol (3% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight) and sterile water (the balance) in a container.
39. A composition suitable for topical application comprising methoxypolyethylene glycol (20% by weight), benzyl alcohol (1% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight), and sterile water (the balance) in a container.
40. The composition of Claim 32, 33, 34, 35, 36, 37, 38 or 39 wherein

the sodium hyaluronate has a molecular weight less than 750,000 daltons.

41. A composition in a container comprising, in a form for topical application,

Sterile Water

Glycerine

Benzyl Alcohol

about 1% by weight of the composition of Diclofenac Sodium

about 3% by weight of the composition of Sodium

Hyaluronate having a molecular weight less than about 750,000 daltons.

42. A composition in a container comprising in a form for topical application,

Glycerine

Benzyl Alcohol

about 3% by weight of the composition of Diclofenac Sodium

about 2.5% by weight of the composition of Sodium Hyaluronate

having a molecular weight less than about 750,000 daltons

Sterile water.

43. A composition in a container comprising in a form for topical application,

Methoxypolyethylene Glycol

Benzyl Alcohol

about 3% by weight of the composition of Diclofenac Sodium

about 2.5% by weight of the composition of Sodium

Hyaluronate having a molecular weight less than about 750,000

daltons

Sterile Water.

44. A composition in a container comprising in a form for topical application,

Sterile Water

a solubilizer

a preservative

about 3 % by weight of the composition of Diclofenac Sodium

about 2.5 % by weight of the composition of Sodium Hyaluronate

having a molecular weight less than about 750,000 daltons.

45. A composition in a container comprising in a form for topical application,

Sterile Water

Meglumine

about 5% by weight of the composition of Ibuprofen

Benzyl Alcohol

Glycerin

about 3% by weight of the composition of Hyaluronate

Sodium having a molecular weight less than about 750,000 daltons.

46. A composition in a container comprising in a form for topical application,

Sterile Water

Meglumine

about 2% by weight of the composition of Piroxicam

about 2.5% by weight of the composition of Hyaluronate Sodium having a molecular weight less than about 750,000 daltons.

47. A composition in a container comprising in a form for topical application an oily phase comprising a
wax and Glycerin and an AQUEOUS PHASE comprising:
Sterile Water
Meglumine
about 5% by weight of the composition of Ibuprofen
about 1.5% by weight of the composition of Sodium Hyaluronate having a molecular weight less than about 750,000 daltons and a Preservative.
48. A composition in a container comprising a form for topical application,
Sterile Water
Glycerin
Benzyl Alcohol
about 1% by weight of the composition of Diclofenac Sodium
about 3% by weight of the composition of Hyaluronate Sodium having a molecular weight less than about 750,000 daltons.
49. A composition in a container comprising in a form for topical application,
Sterile Water
preservative
about 1% by weight of the composition of Diclofenac Sodium

about 3% by weight of the composition of Sodium Hyaluronate having a molecular weight less than about 750,000 daltons.

50. A composition in a container comprising in a form for topical application an oily phase comprising a wax and Glycerine

and an Aqueous Phase comprising,

Sterile Water

Meglumine

about 1.5% by weight of the composition Sodium

Hyaluronate having a molecular weight less than about 750,000 daltons

about 5 % by weight of the composition of Ibuprofen and a preservative.

51. A composition in a container comprising in a form for topical application,

Sterile Water

about 2.5% by weight of the composition of Sodium Hyaluronate having a molecular weight less than about 750,000 daltons

about 1% by weight of the composition of Flunixin and a preservative.

52. A composition in a container comprising in a form for topical application,

between about 1 to about 3% by weight of the composition of Sodium hyaluronic acid having a molecular weight less than about 750,000 daltons,

between about 1 to about 5% by weight of the composition of an NSAID and the balance selected from excipients suitable for topical application and water.

53. The use according to claim 1 wherein the composition comprises
Sterile Water
Glycerine
Benzyl Alcohol
about 1% by weight of the composition of Diclofenac Sodium
about 3% by weight of the composition of Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons
54. The use according to claim 1 wherein the composition comprises
Glycerine
Benzyl Alcohol
about 3% by weight of the composition of Diclofenac Sodium
about 2.5% by weight of the composition of Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons
Sterile water
55. The use according to claim 1 wherein the composition comprises
Methoxypolyethylene Glycol
Benzyl Alcohol
about 3% by weight of the composition of Diclofenac Sodium
about 2.5% by weight of the composition of Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons
Sterile Water

- 152
56. The use according to claim 1 wherein the composition comprises
Sterile Water
a solubilizer
a preservative
about 3 % by weight of the composition of Diclofenac Sodium
about 2.5 % by weight of the composition of Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons
57. The use according to claim 1 wherein the composition comprises
Sterile Water
Meglumine
about 5% by weight of the composition of Ibuprofen
Benzyl Alcohol
Glycerin
about 3% by weight of the composition of Hyaluronate Sodium
having a molecular weight less than about 750,000 daltons
58. The use according to claim 1 wherein the composition comprises
Sterile Water
Meglumine
about 2% by weight of the composition of Piroxicam
about 2.5% by weight of the composition of Hyaluronate Sodium
having a molecular weight less than about 750,000 daltons
59. The use according to claim 1 wherein the composition comprises
wax and Glycerin and an AQUEOUS PHASE comprising:
Sterile Water
Meglumine

about 5% by weight of the composition of Ibuprofen
about 1.5% by weight of the composition of Sodium
Hyaluronate having a molecular weight less than about 750,000
daltons and
a Preservative

60. The use according to claim 1 wherein the composition comprises
Sterile Water
Glycerin
Benzyl Alcohol
about 1% by weight of the composition of Diclofenac Sodium
about 3% by weight of the composition of Hyaluronate Sodium
having a molecular weight less than about 750,000 daltons

61. The use according to claim 1 wherein the composition comprises
Sterile Water
preservative
about 1% by weight of the composition of Diclofenac Sodium
about 3% by weight of the composition of Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons

62. The use according to claim 1 wherein the composition comprises
and an Aqueous Phase comprising,
Sterile Water
Meglumine
about 1.5% by weight of the composition Sodium Hyaluronate
having a molecular weight less than about 750,000 daltons
about 5 % by weight of the composition of Ibuprofen

and a preservative

63. The use according to claim 1 wherein the composition comprises Sterile Water about 2.5% by weight of the composition of Sodium Hyaluronate having a molecular weight less than about 750,000 daltons about 1% by weight of the composition of Flunixin and a preservative
64. The use according to claim 1 wherein the composition comprises between about 1 to about 3% by weight of the composition of Sodium hyaluronic acid having a molecular weight less than about 750,000 daltons, between about 1 to about 5% by weight of the composition of an NSAID and the balance selected from excipients suitable for topical application and water
65. A method of treating a disease and/or condition selected from basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies and/or tumour of the skin, genital warts (condyloma acuminata), cervical cancer, Human Papilloma Virus (HPV), Psoriasis, corns on the feet, hair loss on the head of pregnant women, said method comprising administering topically to the skin and/or exposed tissue of a human, a dosage amount of a pharmaceutical composition, said dosage amount comprising:
- (1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and/or exposed

tissue and;

(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and subunits of hyaluronic acid,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and/or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

66. The method of Claim 65 wherein the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid is hyaluronic acid or a salt thereof.

67. The method of Claim 66 wherein the hyaluronic acid or salt thereof is sodium hyaluronate.

68. The method of Claim 65, 66 or 67 wherein the sodium hyaluronate has a molecular weight less than 750,000 daltons.

69. The method of Claim 65, 66, 67 or 68 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

70. The method of Claim 69 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

71. The method of Claim 69 wherein the NSAID is selected from Ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

72. A method of treating pain topically, said method comprising administering topically to the skin and/or exposed tissue of a human, a dosage amount a pharmaceutical composition, said dosage amount comprising:

(1) a non-steroidal anti-inflammatory drug (NSAID) in a therapeutically effective amount to treat pain of the skin and/or exposed tissue and;

(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and subunits of hyaluronic acid,

characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and/or exposed tissue and in a dosage amount in which component (2) exceeds 10 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of pain to be treated, in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom.

73. The method of Claim 72 wherein component (2) is sodium hyaluronate having a molecular weight less than 750,000 daltons.

74. The method of Claim 72 or 73 wherein component (1) is the non-steroidal anti-inflammatory drug (NSAID), diclofenac.
75. The method of Claim 74 wherein the NSAID is diclofenac sodium.
76. The method of Claim 65, 68 or 72 wherein component (2) is sodium hyaluronate having a molecular weight less than about 750,000 daltons and is in the concentration of $2\frac{1}{2}\%$ by weight of the dosage amount, component (1) is diclofenac sodium and is in the concentration of 3% by weight of the dosage amount, and said dosage amount further comprises a solubilizer for solubilizing the diclofenac, and a preservative.
77. The method of Claim 68 wherein the disease and/or condition is basal cell carcinoma.
78. The method of Claim 68 wherein the disease and/or condition is actinic keratosis lesions.
79. The method of Claim 68 wherein the disease and/or condition is liver spots.
80. The method of Claim 68 wherein the disease and/or condition is squamous cells tumours.
81. The method of Claim 68 wherein the disease and/or condition is metastatic cancer of the breast to the skin.

82. The method of Claim 68 wherein the disease and/or condition is metastatic melanoma in the skin.
83. The method of Claim 68 wherein the disease and/or condition is malignancies and/or tumours of the skin.
84. The method of Claim 68 wherein the disease and/or condition is genital warts.
85. The method of Claim 68 wherein the disease and/or condition is cervical cancer.
86. The method of Claim 68 wherein the disease and/or condition is HPV (Human Papilloma Virus) including HPV of the cervix.
87. The method of Claim 68 wherein the disease and/or condition is psoriasis (both plaque type psoriasis and nail bed psoriasis).
88. The method of Claim 68 wherein the disease and/or condition is corns on the feet.
89. The method of Claim 68 wherein the disease and/or condition is hair loss on the head of pregnant women.
90. A method of accumulating a drug and a form of hyaluronic acid in the skin and/or exposed tissue of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a composition

comprising pharmaceutical excipients suitable for topical applications, an effective non-toxic (to the patient) dosage amount of a drug to treat and to assist to resolve a disease and/or condition of the skin and exposed tissue and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid effective to transport (to facilitate or cause the transport of) the drug percutaneously to the site in the skin including the epidermis or exposed tissue of the disease or condition to accumulate and remain there for a prolonged period of time, wherein the amount of the form of hyaluronic acid administered is at least 5 mg/cm² of skin and/or exposed tissue.

91. The method of Claim 90 where the accumulation takes place in the epidermis.

92. The method of Claim 90 or 91 wherein the hyaluronic acid and salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid is hyaluronic acid or a salt thereof having a molecular weight less than 750,000 daltons.

93. The method of Claim 90, 91 or 92 wherein the disease and/or condition is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours of the skin, primary and metastatic melanoma in the skin, genital warts cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women.

94. A method of accumulating a medicine and/or therapeutic agent (component (1)) and a form of hyaluronic acid (component (2)) in the epidermis of the skin and/or exposed tissue of a human comprising topically administering a therapeutically effective non-toxic dosage amount of a pharmaceutical composition comprising components (1) and (2) characterized in that said dosage amount of said composition is in a dosage form suitable for topical application to the skin and/or exposed tissue and in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates in the epidermis for a prolonged period before passage therefrom, and wherein the pharmaceutical composition further comprising pharmaceutical excipients suitable for topical application.

95. The method of Claim 90, 91, 92, 93 or 94 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight less than 750,000 daltons.

96. A method of rapidly transporting a drug to the epidermis, and accumulating and maintaining the drug therein for a prolonged period of time, the method comprising topically administering a composition comprising together with pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and resolve a disease or condition of the skin and exposed tissue at the site of the trauma and/or

pathology caused by the disease and/or condition), non-toxic (to the patient) dosage amount of a drug and an amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid to facilitate the rapid transport of the drug to the site in the skin or tissue of the disease or condition to the site of the pathology and/or trauma to accumulate there and be retained there for a prolonged period of time and wherein the form of hyaluronic acid is administered in excess of 5 mg. per cm².

97. The method of Claim 96 wherein the hyaluronic acid and salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid is sodium hyaluronate having a molecular weight less than 750,000 daltons.

98. The method of Claim 96 or 97 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

99. The method of Claim 96 or 97 wherein the drug is an anti-cancer drug.

100. The method of Claim 98 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

101. The method of Claim 99 wherein the drug is selected from Novantrone and 5-Fu (FLUORACIL).

102. The method of Claim 98 wherein the NSAID is selected from Ibuprofen piroxicam, acetylsalicylic acid, propionic acid derivatives and

flunixin.

162

103. A method of controlling the unloading of a drug from the skin or exposed tissue of a human suffering trauma and/or pathology, into the lymphatic system comprising delivering (transporting) an amount of drug into the skin or exposed tissue by an effective non-toxic dosage amount of a form of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid to the skin (epidermis) and/or exposed tissue wherein the amount of the form of hyaluronic acid exceeds at least about 5mg./cm².

104. The method of Claim 103 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight less than about 750,000 daltons.

105. The method of Claim 103 or 104 wherein the drug is a drug which inhibits prostaglandin synthesis.

106. The method of Claim 105 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

107. The method of Claim 105 wherein the drug is selected from diclofenac, indomethacin, naproxen and (+/-) tromethamine salt of ketorolac.

108. The method of Claim 105 wherein the drug is selected from Ibuprofen piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

163

109. A method of accumulating a drug in the skin and/or exposed tissue of a human suffering from trauma and/or a pathology comprising topically administering to the skin and/or exposed tissue a composition comprising the drug and an effective non-toxic amount of a form of hyaluronic acid comprising hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid to transport (facilitate or cause the transport of) the drug into the skin and/or exposed tissue wherein the amount of the form of hyaluronic acid exceeds at least about 5 mg/cm² of the surface area of the skin and/or exposed tissue to which the composition is applied.
110. The method of Claim 109 wherein the form of hyaluronic acid is hyaluronic acid and/or salts thereof.
111. The method of Claim 110 wherein the form of hyaluronic acid is sodium hyaluronate having a molecular weight less than about 750,000 daltons.
112. The method of Claim 109, 110 or 111 wherein the drug is a drug which inhibits prostaglandin synthesis.
113. The method of Claim 109, 110 or 111 wherein the drug is a non-steroidal anti-inflammatory drug.
114. The method of Claim 113 wherein the drug is selected from diclofenac, indomethacin, naproxen and (+/-) tromethamine salt of ketorolac.

Ibuprofen piroxicam, acetylsalicylic acid, propionic acid derivatives and flunixin.

116. The use of a dosage amount of a pharmaceutical composition comprising:

(1) a medicinal and/or therapeutic agent for the treatment of a disease or condition of the skin and/or exposed tissue of a human; and

(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and sub-units of hyaluronic acid

for the treatment topically of basal cell carcinoma, actinic keratoses, liver spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma of the skin, malignancies and/or tumour of the skin, genital warts (condyloma acuminata), cervical cancer, Human Papilloma Virus (HPV), psoriasis, corns on the feet, and hair loss on the head of pregnant women wherein the dosage amount is in a dosage form suitable for topical application to the skin and/or exposed tissue of a human and in a dosage amount in which component (2) exceed 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is applied.

117. The use of a dosage amount of a pharmaceutical composition comprising:

(1) a non-steroidal anti-inflammatory drug (NSAID) for the treatment of pain of the skin and/or exposed tissue of a human; and

(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and sub-units of hyaluronic acid

for the topical treatment of pain in the skin and/or exposed tissue of a human wherein the dosage amount is in a dosage form suitable for topical application and in a dosage amount in which component (2) exceeds 10 mg/cm² of the skin or exposed tissue to which the dosage amount is applied.

118. The use of Claim 116 wherein component (2) is sodium hyaluronate having a molecular weight less than 750,000 daltons.

119. The use of Claim 117 wherein component (2) is sodium hyaluronate having a molecular weight less than 750,000 daltons.

120. The use of Claim 118 or 119 wherein the sodium hyaluronate has a molecular weight between 150,000 daltons and 225,000 daltons.

121. The use of Claim 116, 117, 118, 119 or 120 wherein the pharmaceutical composition contains suitable topical excipients.

122. The use of Claim 116, 117, 118, 119, 120 or 121 wherein component (1) is the non-steroidal anti-inflammatory drug (NSAID), diclofenac.

123. The use of Claim 122 wherein the NSAID is diclofenac sodium.

124. The use of Claim 116, 117, 118, 119, 120 or 121 wherein component (1) is an anti-cancer agent.

125. The use of Claim 124 wherein the anti-cancer agent is novantrone.
126. The use of Claim 123 wherein the concentration of the diclofenac sodium is 3%, component (2) is sodium hyaluronate in a concentration of $2\frac{1}{2}\%$ by weight of the dosage amount and said dosage amount further comprises a solubilizer for solubilizing the diclofenac sodium, and a preservative.
127. The use of Claim 116 or 118 wherein the disease and/or condition is basal cell carcinoma.
128. The use of Claim 116 or 118 wherein the disease or condition is actinic keratoses.
129. The use of Claim 116 or 118 wherein the disease or condition is liver spots.
130. The use of Claim 116 or 118 wherein the disease or condition is squamous cell tumours.
131. The use of Claim 116 or 118 wherein the disease or condition is metastatic cancer of the breast to the skin.
132. The use of Claim 116 or 118 wherein the disease or condition is primary and metastatic melanoma of the skin.
133. The use of Claim 116 or 118 wherein the disease or condition is

malignancies and/or tumour of the skin.

134. The use of Claim 116 or 118 wherein the disease or condition is genital warts (condyloma acuminata).

135. The use of Claim 116 or 118 wherein the disease or condition is cervical cancer.

136. The use of Claim 116 or 118 wherein the disease or condition is Human Papilloma Virus (HPV).

137. The use of Claim 116 or 118 wherein the disease or condition is psoriasis.

138. The use of Claim 116 or 118 wherein the disease or condition is corns on the feet or the hair loss on the head of pregnant women.

139. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

3% by weight of the composition of Glycerine

1.5% by weight of the composition of Benzyl Alcohol

1% by weight of the composition of Diclofenac Sodium

3% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 661,600 daltons

3% by weight of the composition of Liquid Wax and

Sterile Water

characterized in that the said pharmaceutical composition is 1500 gm, said

composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation in the epidermis before passage therefrom.

140. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

5% by weight of the composition of Glycerine

3% by weight of the composition of Benzyl Alcohol

3% by weight of the composition of Diclofenac Sodium

2.5% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 661,600 daltons and

Sterile Water

characterized in that the said pharmaceutical composition is 3,000 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for

accumulation therein in the epidermis before passage therefrom.

141. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

20% by weight of the composition of Methoxypolyethylene Glycol

1% by weight of the composition of Benzyl Alcohol

3% by weight of the composition of Diclofenac Sodium

2.5% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 679,000 daltons and

Sterile Water

characterized in that the said pharmaceutical composition is 1,600 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

142. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

20% by weight of the composition of a solubilizer,

Methoxypolyethylene Glycol

1% by weight of the composition of a preservative,

Benzyl Alcohol

3% by weight of the composition of Diclofenac Sodium

2.5% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 679,000 daltons, and

Sterile Water

characterized in that the said pharmaceutical composition is 1,600 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

143. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

5.5% by weight of the composition of Meglumine

5% by weight of the composition of Ibuprofen

1% by weight of the composition of Benzyl Alcohol

1% by weight of the composition of Glycerin

3% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 661,600 daltons, and

Sterile Water

characterized in that the said pharmaceutical composition is 227 gm, said

composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

144. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

4% by weight of the composition of Meglumine

2% by weight of the composition of Piroxicam

- 2.5% by weight of the composition of Sodium Hyaluronate
having a molecular weight of 661,600 daltons, and

Sterile Water

characterized in that the said pharmaceutical composition is 217 gm; said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

145. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

an oily phase comprising:

15% by weight of the composition of a liquid wax

16% by weight of the composition of a wax

5% by weight of the composition of Glycerin

and an aqueous phase comprising:

5% by weight of the composition of Meglumine

5% by weight of the composition of Ibuprofen

1.5% by weight of the composition of Sodium Hyaluronate

having a molecular weight of 200,000 daltons and

0.3% by weight of the composition of a preservative,

Suttocide A

and Sterile Water

characterized in that the said pharmaceutical composition is 3,384 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

146. A multidose multigram pharmaceutical composition for topical

application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

- 3% by weight of the composition of Glycerin
- 1.5% by weight of the composition of Benzyl Alcohol
- 3% by weight of the composition of Liquid Wax
- 1% by weight of the composition of Diclofenac Sodium
- 3% by weight of the composition of Sodium Hyaluronate having a molecular weight of 679,000 daltons, and Sterile Water

characterized in that the said pharmaceutical composition is 3,100 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

147. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

- 1.5% by weight of the composition of a preservative, Benzyl Alcohol
- 3% by weight of the composition of Glycerin
- about 1% by weight of the composition of Diclofenac Sodium
- 3% by weight of the composition of Liquid Wax

74
3% by weight of the composition of Sodium Hyaluronate
having a molecular weight is 661,600 daltons, and
Sterile Water

characterized in that the said pharmaceutical composition is about 1,550 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

148. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

an oily phase comprising 15% by weight of the composition
of a liquid wax,
16% by weight of a wax and
5% by weight of the composition of Glycerine
and an Aqueous Phase comprising
5% by weight of the composition of Meglumine
1.5% by weight of the composition of Sodium Hyaluronate
having a molecular weight 207,000 daltons
5% by weight of the composition of Ibuprofen and a
0.3% by weight of the composition a preservative,
Suttocide, and

175
Sterile Water

characterized in that the said pharmaceutical composition is 3,385 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

149. A multidose multigram pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising:

2.5% by weight of the composition of Sodium Hyaluronate
having a molecular weight is 661,600 daltons

1% by weight of the composition of Flunixin Meglumine and
Sterile Water

characterized in that the said pharmaceutical composition is 3,000 gm, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an effective dosage amount exceeding 5 mg/cm² of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for

176

accumulation therein in the epidermis before passage therefrom.

Dated 20 October, 1997
Norpharmco Inc.

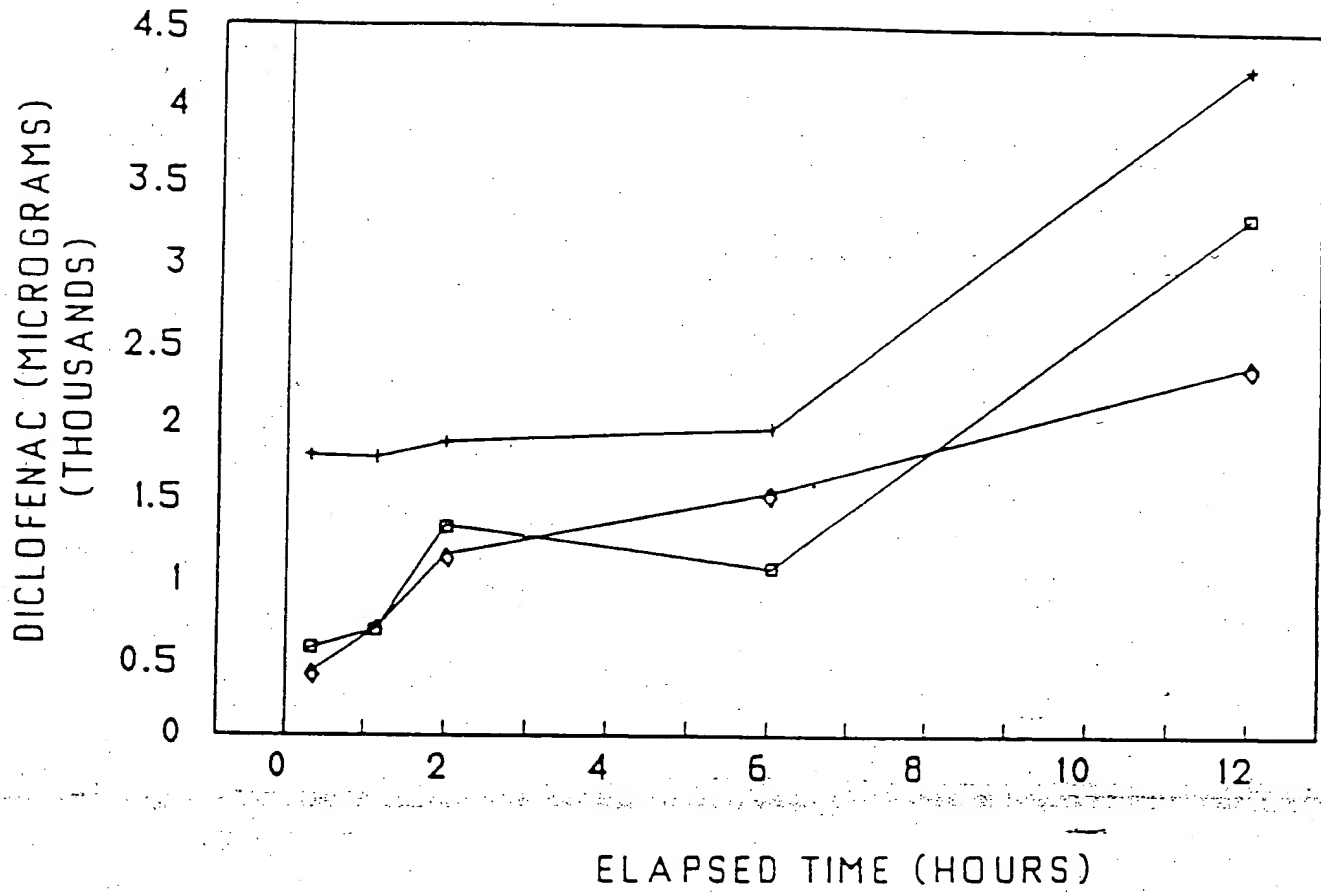
Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

Topical Composition Containing Hyaluronic Acid and NSAIDS

Abstract

A pharmaceutical composition from which effective non-toxic dosage amounts may be taken and applied to the skin or exposed tissue of a human, each effective dosage
5 amount comprising pharmaceutical excipients suitable for topical application, an effective non-toxic dosage amount of a non-steroidal anti-inflammatory drug to treat a disease or condition of the skin or exposed tissue of a human involving a pathology and an effective non-toxic dosage amount of a form of hyaluronic acid selected from the group consisting
10 of hyaluronic acid and its non-toxic salts and combination thereof sufficient to transport the drug percutaneously into the skin or exposed tissue to accumulate and remain in the epidermis for a prolonged period of time and which is systemic independent acting and wherein said pharmaceutical composition comprises 3% by weight of the drug and 2.5% by weight of the form of hyaluronic acid having a molecular weight less than 750,000 daltons and greater than 150,000 daltons.

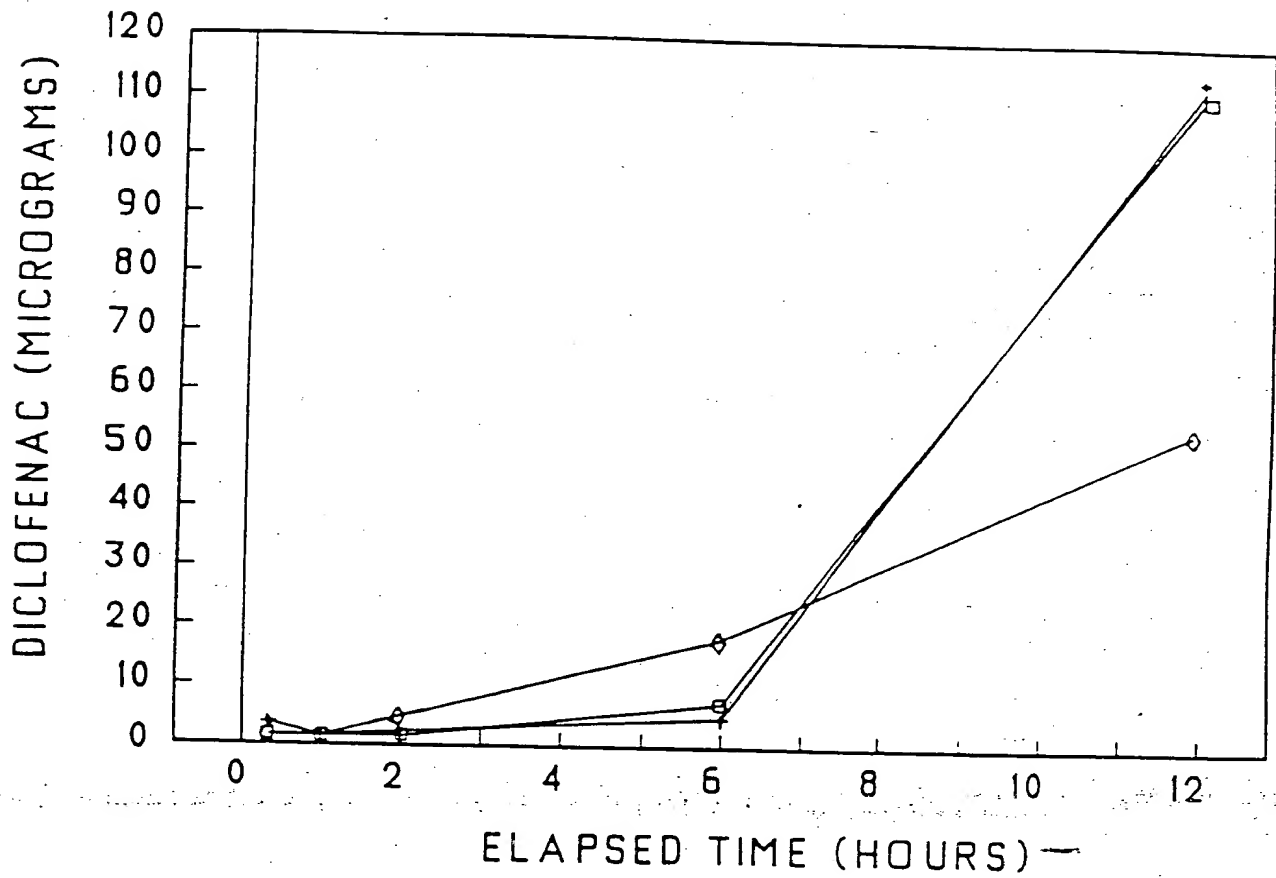
1/12



□ 0604001093 + EPDICLO1 ♦ XP8049

FIG.1.

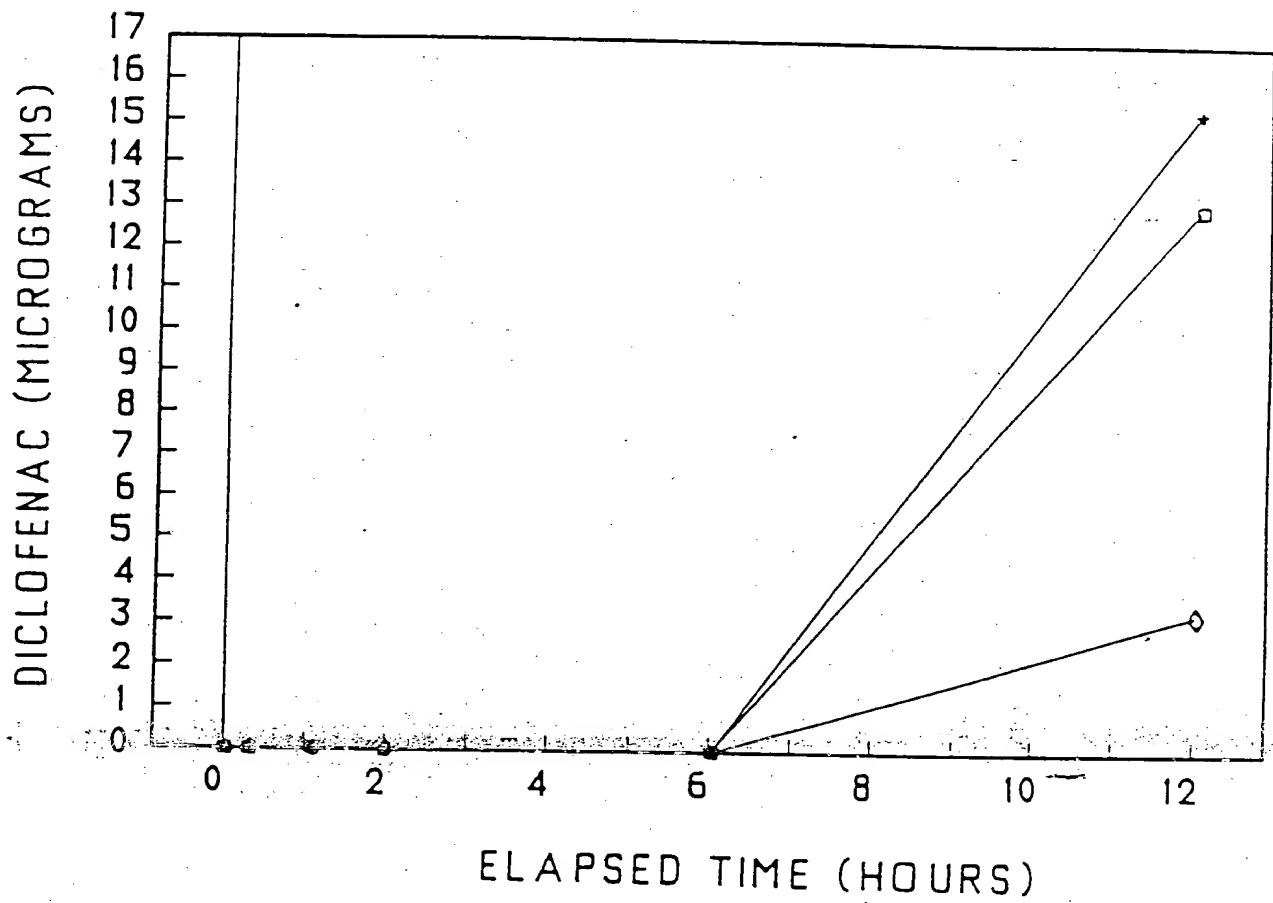
2/12



□ 0604001093 + EPDICLO1 ♦ XP8049

FIG 2'

3/12



□ 0604001093 + EPDICLO1 ♦ XP8049

FIG.3'

4/12

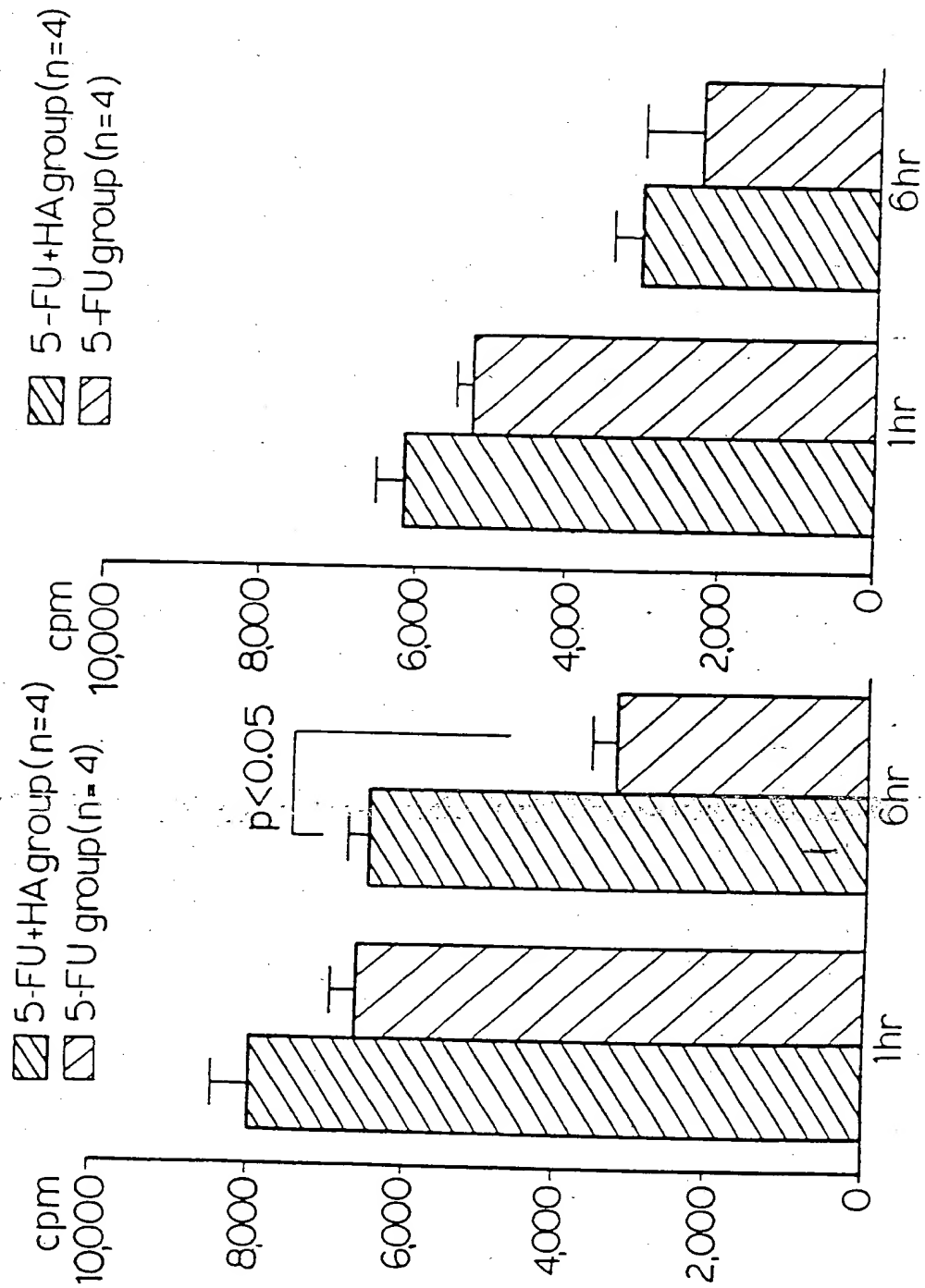


FIG 4'

5/12

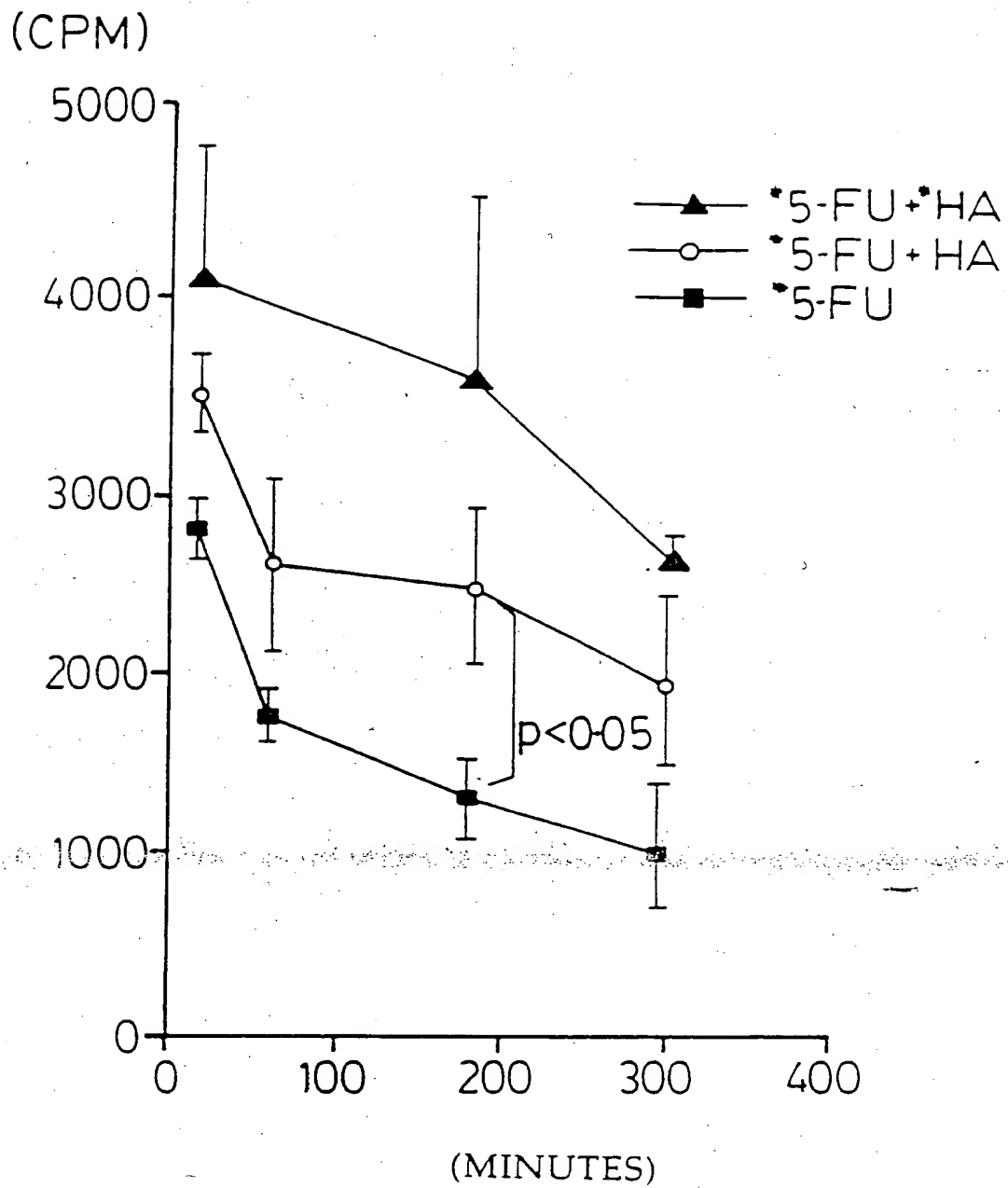


FIG. 5'

6/12

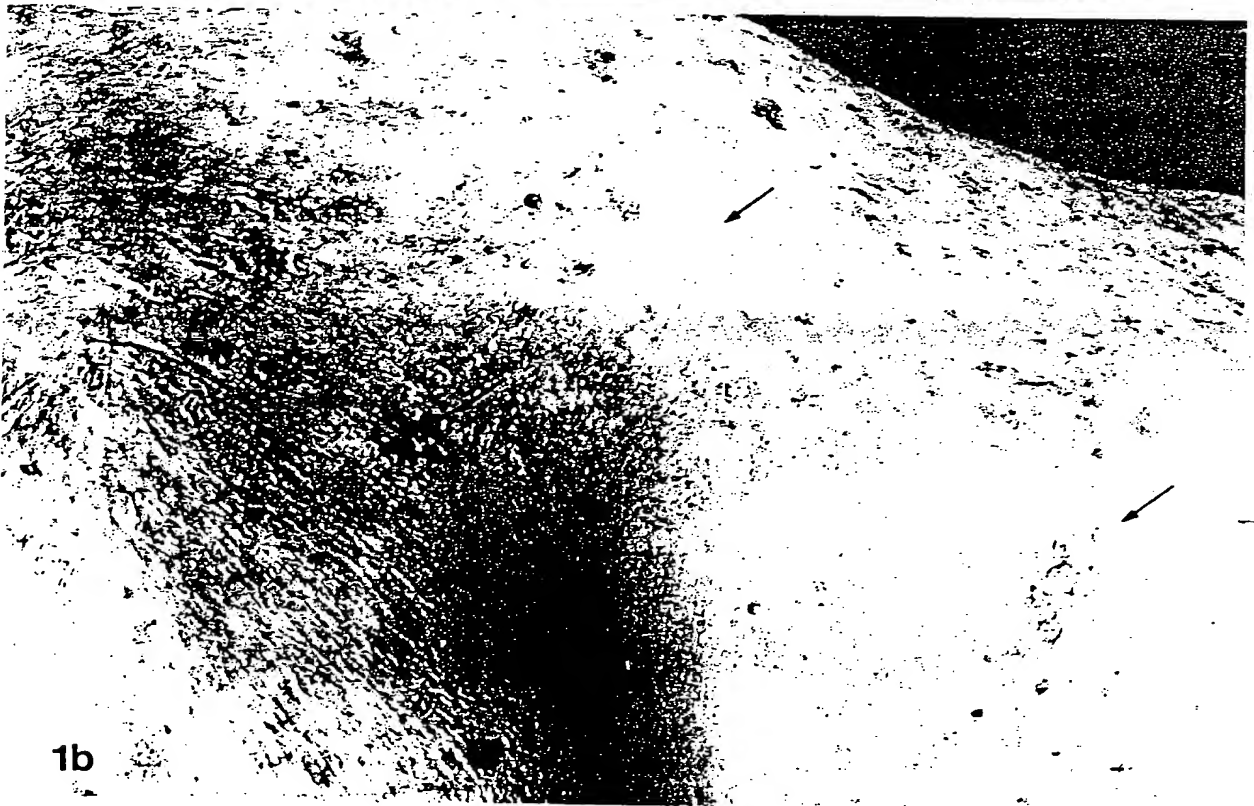
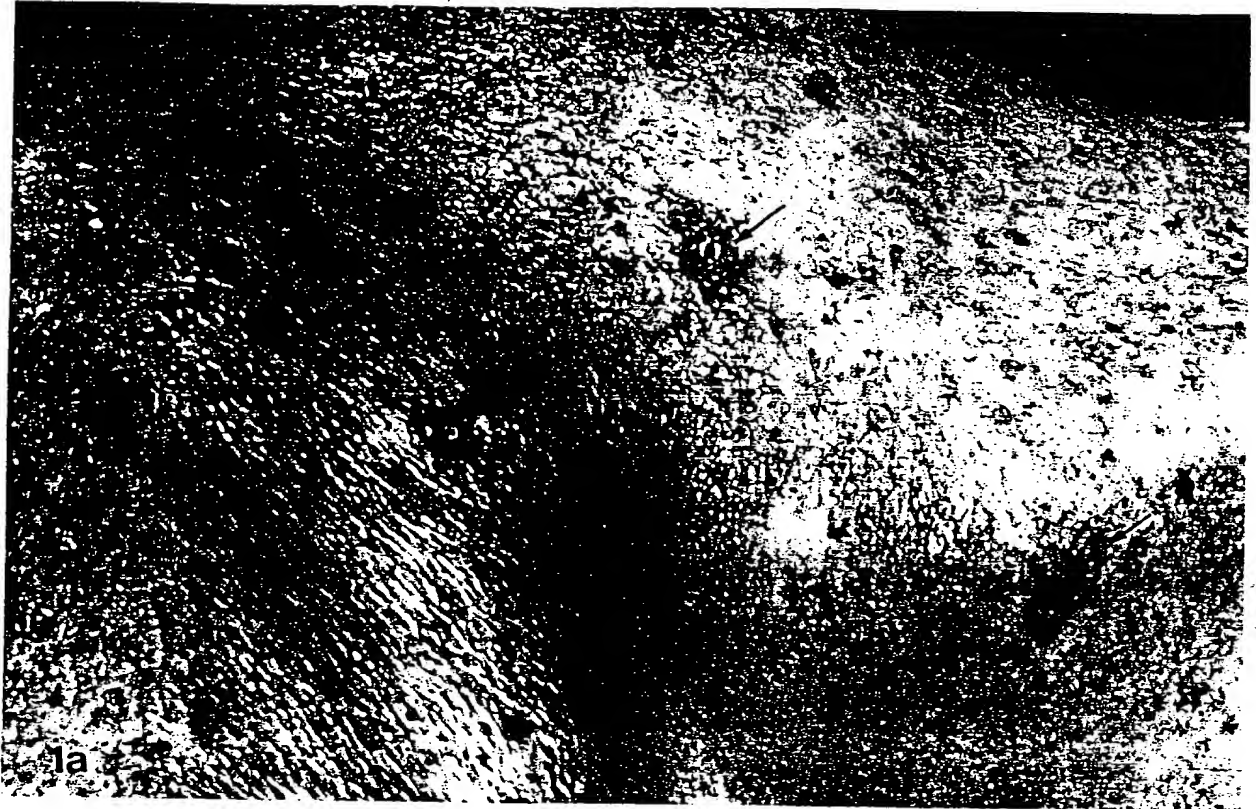


FIGURE 6

7/12

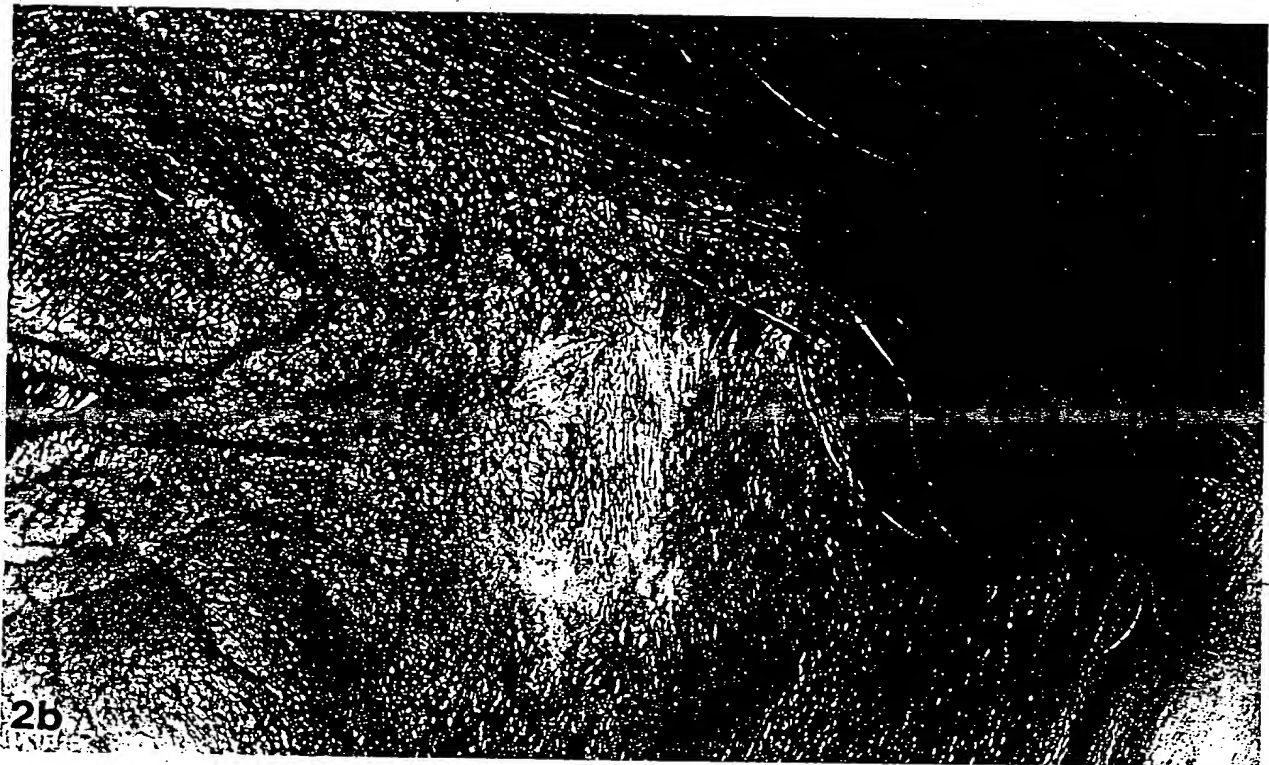
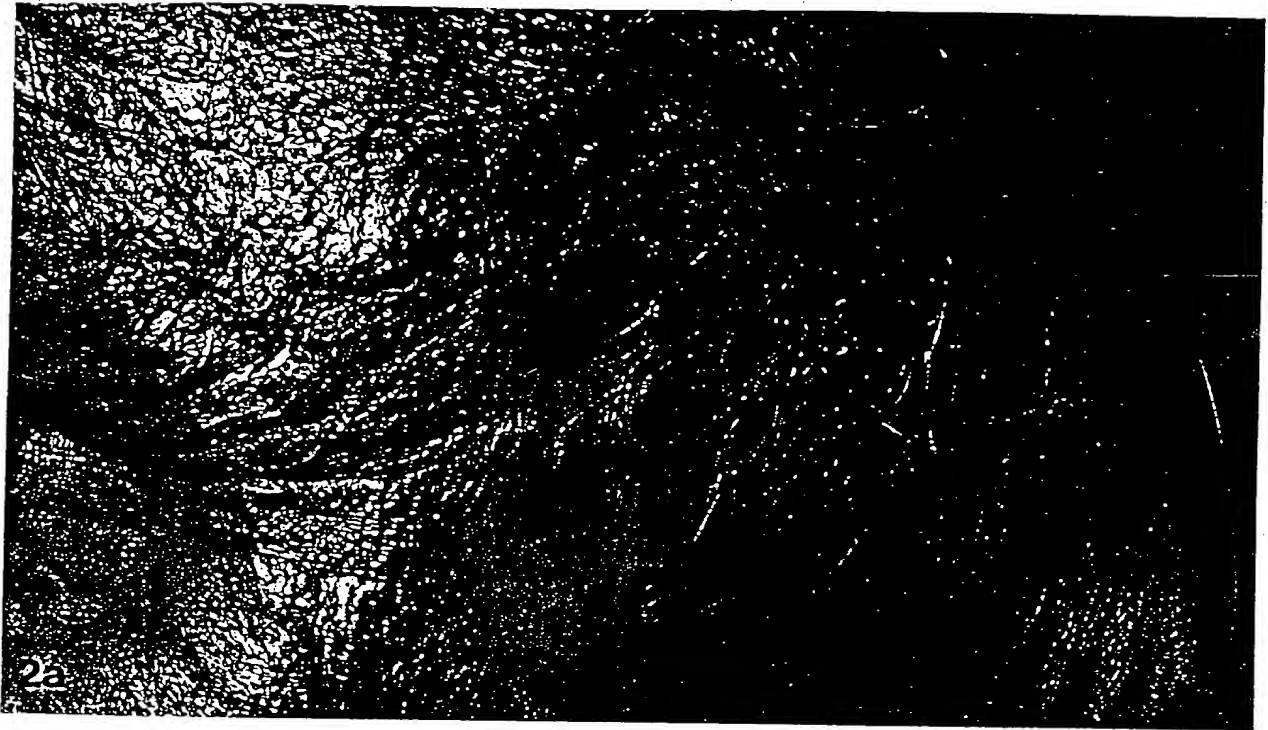


FIGURE 7

8/12

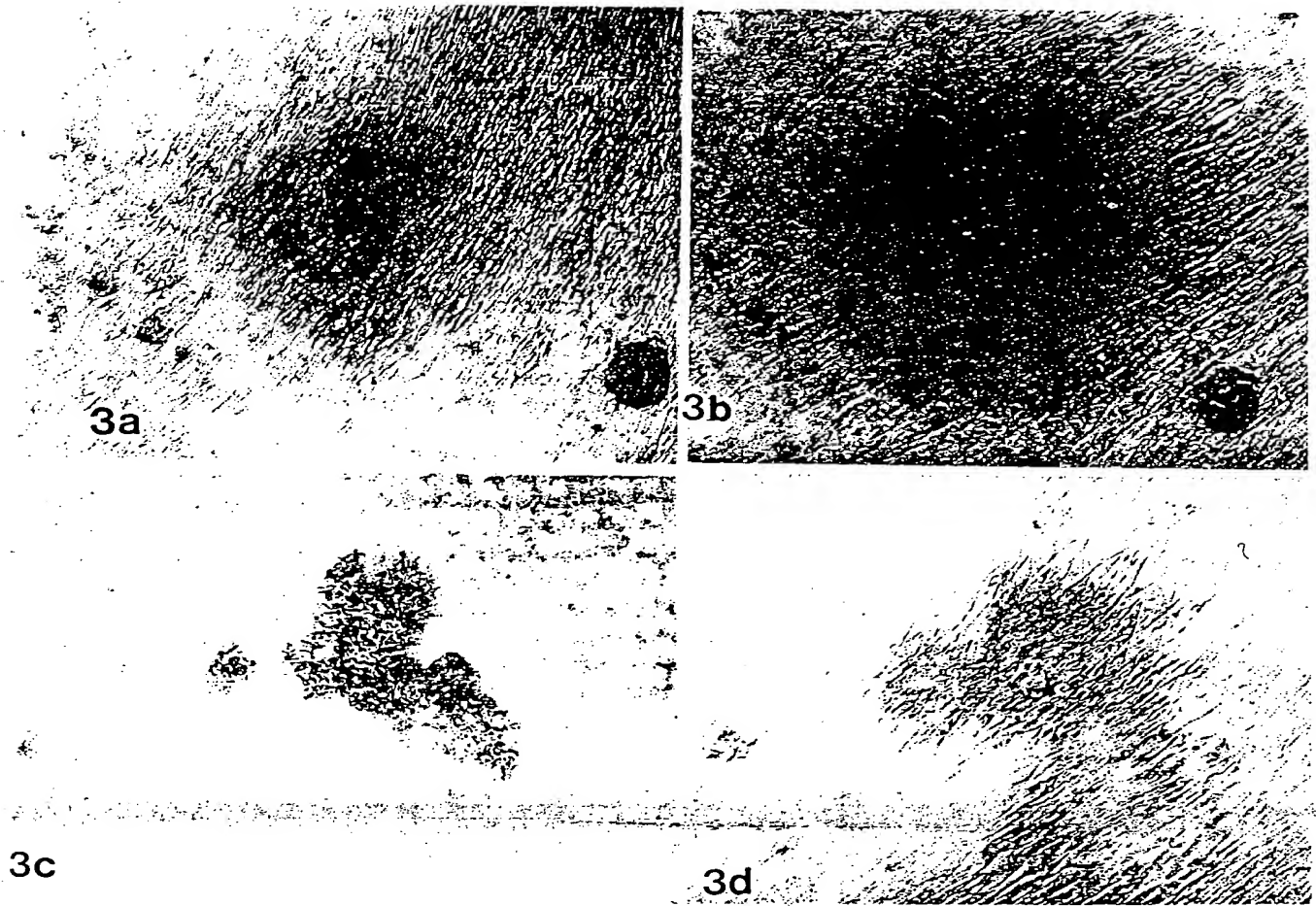


FIGURE 8

9/12

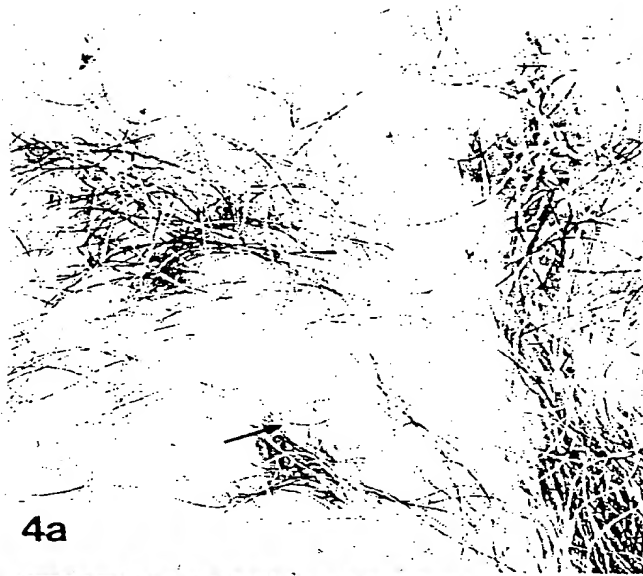


FIGURE 9

10/12

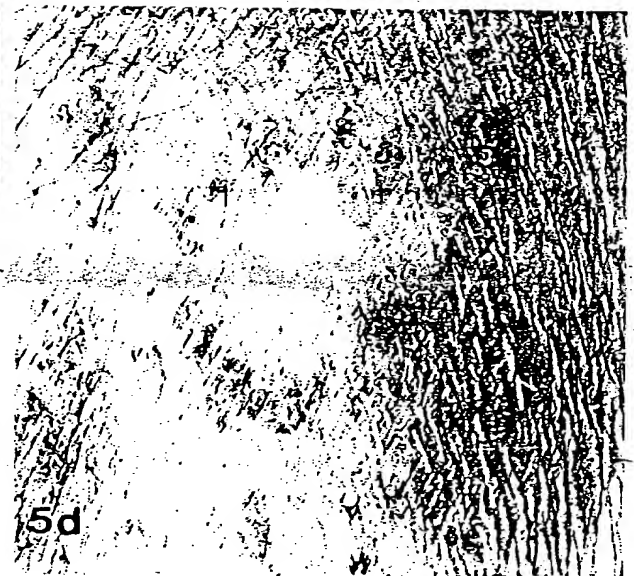
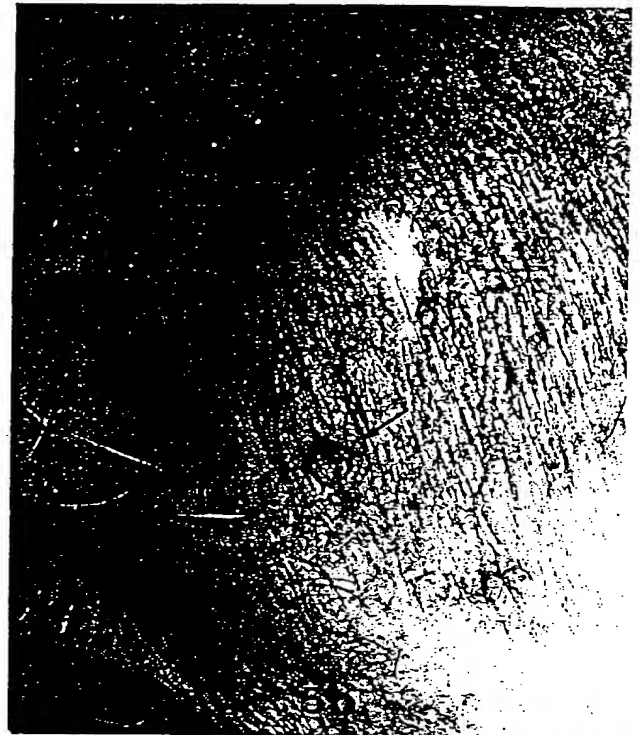


FIGURE 10

11/12

6a



6b



6c



FIGURE 11

12/12

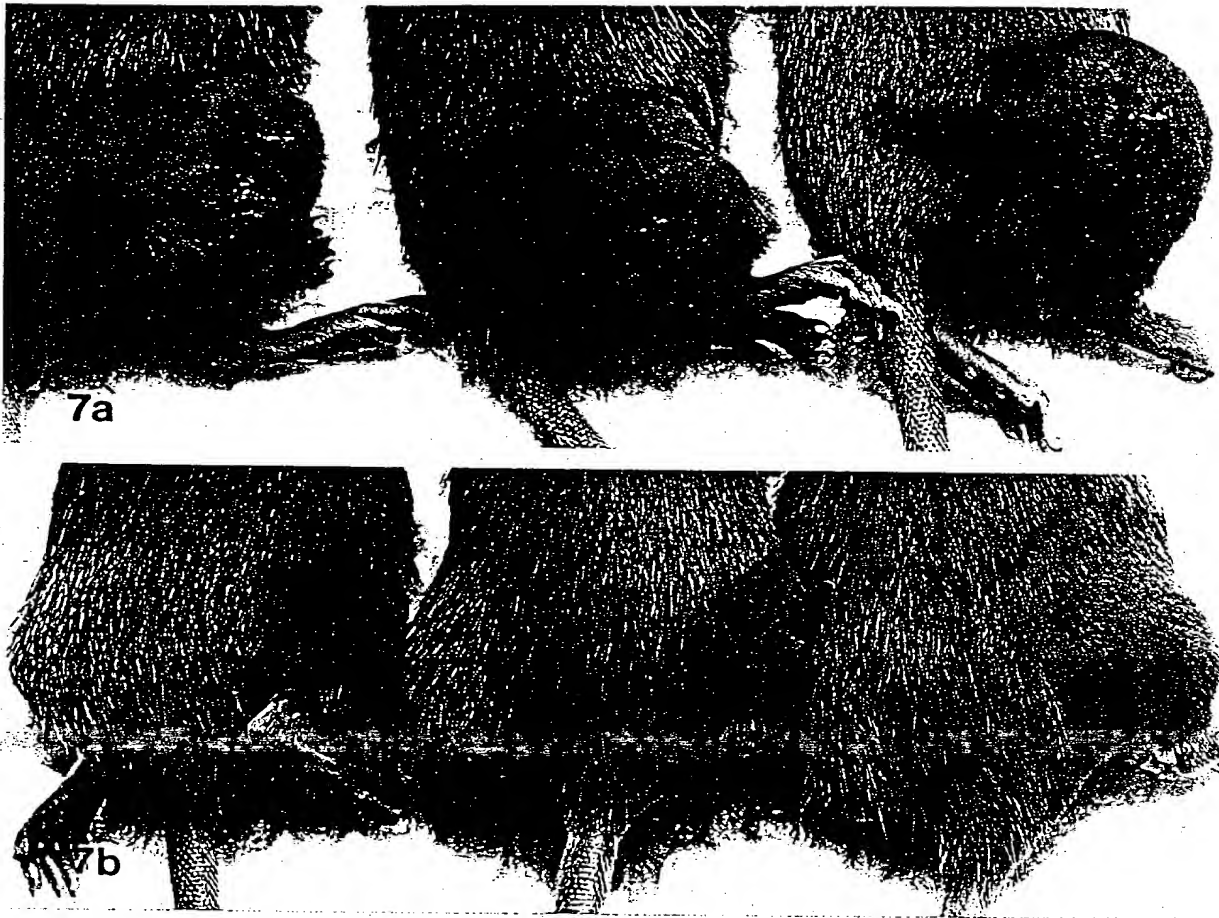


FIGURE 12

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